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Belinda Rivera-Lebron
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Pulmonary Embolism

From Acute PE to Chronic Complications

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Epidemiology of Pulmonary Embolism

Rami Alashram, Eneida Male, and Parth Rali

Abbreviations

CTPA	CT pulmonary angiogram
CVC	Central venous catheter
DALYs	Disability-adjusted life-years
HRT	Hormone-replacement therapy
NIS	National inpatient sample
OCP	Oral contraceptive pill
PE	Pulmonary embolism
VT	Venous thromboembolism

Introduction

Venous thromboembolism (VTE) is a major contributor to the global disease burden [1]. Pulmonary embolism (PE) is the third most common cardiovascular disease after stroke and myocardial infarction [2]. In 2006, 247,000 adults were hospitalized in the United States with acute PE [3]. VTE is the leading cause of lost disability-adjusted life-years (DALYs) lost in low- and middle-income countries and the second leading cause in high-income countries. A recent study involving 35.4 million hospitalized patients (>48 hours) found that more than half of hospitalized patients are at risk of VTE development [4].

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Incidence and Prevalence of PE

The true incidence of PE remains unknown as sudden death before clinical presentation is common (up to 25%) [5] and nearly half of all cases are not diagnosed [6]. A 1982 autopsy study on 1455 patients before the era of CT pulmonary angiogram (CTPA) showed that only 30% of patients with an anatomically major PE were correctly diagnosed antemortem [7]. Autopsy studies have also shown that between 5% and 10% of all in-hospital deaths are a direct result of PE [8–10]. US historical data demonstrated an increase in the incidence rate of VTE from 23 cases per 100,000 to 770 cases per 100,000 from 1986 to 2005 [3, 11]. The annual worldwide VTE incidence rates range from 0.75 to 2.69 per 1000 individuals in the population [1]. In the USA, the Surgeon General's report estimated that more than 350,000 individuals are affected by VTE each year [12]. With regard to PE specifically, several North American population cohorts have reported a variety of population incidence rates. In a cohort study of 2218 patients who resided within Olmsted County, Minnesota, were followed up over a 25-year period from 1966 through 1990. The overall average age- and sex-adjusted annual incidence of PE then was reported to be 69 per 100,000 [13]. A Canadian population study from Québec conducted between 2000 and 2009 reported the age- and sex-adjusted incidence rate of definite or probable PE to be 0.45 per 1000 person-years [14]. Another Canadian study conducted from 2002 to 2012 reported the age- and sex-adjusted incidence rate of PE to be 0.38 per 1000 person-years [15].

Reported trends of PE incidence have varied. Some studies have found that the incidence of PE has remained relatively stable over time [13, 15, 16]; while others have reported a period of increased incidence in the 1990s [17–19]. A study based on National US inpatient sample (NIS) data revealed that admissions for acute PE have increased from 60,000 in 1993 (23 per 100,000) to more than 202,000 in 2012 (65 per 100,000), but the proportion of patients with massive PEs have decreased from 5.3% to 4.4% [19]. Increased incidence of PE coincided with the introduction of CTPA into routine clinical practice. This effect was demonstrated by a study that showed an 81% increase in the age-adjusted incidence of PE after the introduction of CTPA [from 62.13 per 100,000 (1993–1998) to 112.3 per 100,000 (1998–2006)] [18]. Pennsylvania Health Care Cost Containment Council PE discharge data (1997 to 2001) showed CTPA scans had increased from 23.23% to 45.18% compared to other procedures [20] The PE-related length of stay is decreasing while the cost of care is increasing. An NIS study from 1993 to 2012 revealed that the median length of stay has decreased from 8 days (interquartile range [IQR], 6–11) to 4 days (IQR, 3–6) days ($P < 0.001$) and the adjusted hospital charges have increased from $16,475 (IQR, $10,748–$26,211) in 1993 to $25,728 (IQR, $15,505–$44,493) in 2012 ($P < 0.001$) [19] This probably is related to overuse of CTPA that leads to diagnosis of non-clinically significant small PEs and subsequent hospital admissions and further testing.

Age, Gender, and Ethnicity

The incidence of PE increases dramatically with age [1] while recurrent PEs are more common in younger patients [21]. PE has been previously reported to occur more frequently in women and this was attributed to estrogen use, childbearing, and a higher frequency of DVT [22–26]. Other studies have reported an increased incidence in men [11, 13, 27]. More recent studies have swung back and reported an increased incidence of PE in females. A population study from Norway conducted between 1995 and 2001 demonstrated that the incidence for first VTE events was slightly higher in women than in men [28]. Statewide PE discharge data (1997–2001) from the Pennsylvania Health Care Cost Containment Council reported that PE incidence is higher in female patients (0.013% higher than for male patients) [20]. The National Hospital Discharge Survey conducted in 1999 reported that the rate of diagnosis of PE in 1999, not adjusted for age, was higher in women (60 per 100,000 women/year vs. men 42 per 100,000 men/year), but the age-adjusted rates of diagnosis of PE per 100,000 population in that study for men and women were similar [29].

In a systematic review of the annual worldwide VTE incidence rates, individuals of Korean and Chinese ethnicity were found to have less incidence rates [1]. The prevalence of PE in hospitalized patients has been reported to be lower among Asians/Pacific Islanders (0.1/100 hospitalizations) than among whites (0.4/100 hospitalizations) and African Americans (0.4/100 hospitalizations) [30]. In the USA, the incidence of PE among whites and blacks has been inconsistent. Stein et al. found that the rates of diagnosis were similar among blacks and whites if not adjusting for age; but with age adjustment, the rate of diagnosis of PE among blacks was higher when compared to whites (56 per 100,000/year vs. 40 per 100,000/year) [31]. DeMonaco et al. also reported a higher incidence of PE in blacks [20]. The NIS study from 1993 to 2012 revealed that the majority of PE hospitalizations were white [19].

PE-Related Mortality

A National Center for Health Statistics study analyzed US death certificate data from 1979 to 1998 and showed that 1.3% of all deaths had PE listed on their death certificate, and in 33.9% of those PE was the underlying cause of death [32]. Studies have clearly demonstrated that PE mortality increases with age, with risk of death doubling with each decade of life [14, 15, 33]. Men were found to have higher PE mortality rates irrespective of their race or ethnicity when compared to their counterpart ethnic females [32, 33]. African Americans had higher PE mortality rates than whites, and whites had higher mortality rates than minorities (Asian, American Indian, etc.) [32].

PE mortality rates were increasing in the 1962–1984 period but have been decreasing ever since then [34]. Age-adjusted PE death rates decreased from 191 per million in 1979 to 94 per million in 1998 [32]. A more recent study on the national US inpatient data from 1993 to 2012 revealed that all-cause hospital mortality rates for PE admissions had decreased from 7.1% to 3.2% [19]. PE-related mortality had decreased among all races and ethnic groups, with the highest age-adjusted reduction in mortality among black men [33].

Reported 30-day PE case-fatality rates range from 3.9% to 19.1% [15, 28]. The 30-day and 1-year case-fatality rates are higher in patients with PE than in patients with DVT (9.7% vs. 4.6% for 30-day case-fatality, and 12.9% vs. 7.8% for 1-year case-fatality rates) [15, 28]. Thirty-day case-fatality rates are higher in patients with PE and cancer than in patients with PE without cancer (19.1% vs. 3.6%) [28]. The ICOPER registry showed that PE case-fatality rates are higher in hemodynamically unstable patients (58.3%) than in hemodynamically stable patients (15.1%) [35]. The presence of right ventricular dysfunction was also associated with higher case fatality at 2 weeks and 3 months [35]. A National US inpatient data study from 1993 and 2012 revealed that mortality rates for massive PE were higher (44%) than non-massive PE (2.7%), but overtime both mortality rates have also decreased [19].

Impact of VTE Risk Factors on PE Epidemiology

Obesity (BMI of 30 kg/m^2 or higher) has been shown from a systematic review, as well as cohort and case-control studies, as a potential predisposing factor for PE and DVT in men and women with a relative risk of 2.21 [36, 37]. Height has been associated with an increased risk of VTE in several epidemiologic prospective cohort studies [38, 39]. Data from a Swedish registry revealed that when compared with the tallest women (>1.85 m) and men (>1.9 m), there was graded decreased risk by lower height for both men and women. Overall, the risk was the lowest for the women and men with the shortest stature (<1.55 m and <1.6 m, respectively): hazard ratio = 0.31 and 0.35 [40]. Association with increased height and VTE appears to be related to having a greater venous surface area, a higher number of venous valves, or greater hydrostatic pressure [41].

There is a weak association between immobility from long-distance travel and development of asymptomatic VTE which is confined to asymptomatic calf vein thrombosis in passengers. Overall, long-distance travel increases the risk of VTE by approximately threefold. There is a positive correlation between travel duration and risk of VTE with an 18% additional risk for each two-hour increment increase in travel duration [42]. The risk of a symptomatic PE is less than 0.5 per million passengers and the risk of a fatal PE is 1.65 per 10^6 for flights over 8 hours [43].

Overall, there is a 20-fold increased risk of VTE after a major general surgery (abdominal or thoracic operations that require general anesthesia lasting ≥30 minutes) [44]. The increased risk is thought to be due to increased immobility during and after surgery as well as by direct venous injury and inflammation during surgery [45]. Lower extremity orthopedic operations carry a particularly high risk. Without

the use of prophylaxis, approximately half of the patients undergoing elective total hip or knee replacement develop VTE [46]. Additionally, the bariatric surgical population is particularly at a high risk for VTE; the reported rates of VTE are 0.3–2.2% with rates of PE being approximately 1%, despite application of methods to prevent these complications [47–49]. The incidence of DVT within 3 months of spinal cord injury is 38%, corresponding to a PE frequency of approximately 5%. This risk appears to be the greatest in the initial 2 weeks after surgery; the risk of fatal PE is rare after 3 months of injury [50, 51]. One of these studies quoted the incidence of DVT was 56% in patients with lower limb orthopedic or pelvic injury, and 40% in patients whom the primary site of injury was the face, chest, or abdomen [52].

Pregnancy-related VTE remains one of the leading causes of maternal mortality in the developed world [53]. In a 30-year population study, the overall incidence of VTE during the pregnancy and the post-partum period was found to be 199 per 100,000 woman-years (absolute risk) with a relative risk of 4.29. PE was found to be less common than DVT during this period (47.9 vs. 151.8 per 100,000 woman-years). PE was found to be much more common during the postpartum period compared to the pregnancy period (159.7 vs. 10.6 per 100,000 woman-years). The overall incidence of PE during the pregnancy period remained constant during the 30-year study period, whereas the postpartum incidence of PE decreased by more than twofold [33]. The magnitude of risk in pregnant women is amplified by smoking, inherited thrombophilia, and prior VTE. The risk is 38% higher for women 35 years of age and older and 64% higher for African American women [54]. The greatest risk occurs during the postpartum period [55]. The risk of VTE in female patients taking combined oral contraceptive pills (OCP) is low (10–15 VTE/10,000 women). Women taking high preparations of OCP (>50 μg ethinyl estradiol with levonorgestrel) as well as women taking first- and third-generation progestins may be at a slightly higher risk of VTE. Other factors that may alter this risk in the population include smoking, age, and obesity. For females who are smokers and are on OCP, the risk of VTE is almost doubled than who are on OCP only. Heavy smokers have increased risk compared to light smokers in patients who are on OCP [56]. The dose of estrogen in hormone-replacement therapy (HRT) is 20–25% of that contained in modern OCP [57]. Despite the lower biological potency, women taking HRT have a two- to fourfold increased risk of VTE compared to women who are not taking HRT [58]. Susceptibility to DVT or PE seemed to be the highest during the first year of hormone use.

Similar to women, men receiving estrogen therapy are at increased risk for VTE [59]. Recent literature shows that there is low certainty in the association between testosterone use and VTE in men; these results apply to both transdermal and intramuscular modes of administration [60]. Tamoxifen has been associated with an increased risk of VTE, of two- to threefold in patients treated with tamoxifen compared to placebo [61].

Patients with inherited thrombophilia have a relative risk of 2–11; the actual risk remains relatively modest [62]. The strongest risk factors include hereditary deficiencies of anti-thrombin 3, protein C, and protein S, whereas heterozygous prothrombin 20210A and high factor VIII levels were milder risk factors [63]. Although the genetic risk factors may contribute to the increased likelihood of the initial VTE

which typically happens before the age of 45, they have little impact on the risk of recurrent VTE [64] (Fig. 1).

Central venous catheters (CVC) account for around 9% of all incidental VTE occurring in the community [66]. The proposed direct mechanism is thought to be due to the catheter prompting the fibrin and coagulation factors to attach to vessel wall and propagate [67]. Other contributing factors include presence of prothrombotic factors, underlying disease, and CVC-related characteristics such as the type of material that CVC is composed of, number of lumina, location tip, entry site, and duration of stay [68].

There is a weak association between varicose veins and VTE, and furthermore the risk is found to be decreasing with age [69, 70]. Congestive heart failure is an independent and major risk factor for VTE in both hospitalized and outpatients [71]. VTE occurring in patients with heart failure carries a worse prognosis. Patients with chronic obstructive pulmonary disease have approximately twice the risk of PE and VTE events compared to subjects with normal airflow [72]. This has been speculated to be due to immobilization, heightened systemic inflammation, cigarette smoking, and venous stasis [73, 74]. Asthmatics are at increased risk of VTE with adjusted odds ratio for PE of 1.43, for DVT of 1.56 and for combined PE and DVT of 1.6 [75]. Oral corticosteroids and the presence of severe asthma is an independent risk factor [76, 77]. Patients with ischemic strokes are thought to have threefold higher risk of VTE compared to controls due to limb paralysis, prolonged bed rest, and increased prothrombotic activity [78, 79]. Population studies have revealed that the risk of VTE is higher for hemorrhagic strokes compared to ischemic stroke [79, 80].

Cancer is a strong and independent risk factor for VTE [81]. Active malignancy accounts for almost 20% of all incident VTE occurring in the population [82, 83]. The prevalence appears to be higher in patients with malignancy involving the brain, pancreas, ovary, colon, lung, stomach, kidney, bone, and in patients with distant metastatic sites [84]. Furthermore, data from the REITE registry have shown that cancer patients are particularly at high risk of PE-related death with an absolute PE-related rate of 1.4 [85]. Inflammation appears to change the hemostatic balance in a thrombogenic direction; as such various autoimmune diseases are linked to an

Thrombophilia	Annual Risk of Initial DVT	Relative risk (compared to control)	Recurrent Risk
Anti thrombin Deficiency Protein C Deficiency Protein S Deficiency	1.52-1.90%	15-19x	5 years-40% 10 years-55%
Factor V Leiden Prothrombin 20210A High Factor VIII	0.34-0.49%	3-5x	5 years-11% 10 years-25%
High Factor IX High Factor XI Hyperhomocysteinemia	Not independent risk factors for venous thrombosis. Risk associated with high factor VII		

Fig. 1 Thrombophilias and risk for VTE [63, 65]

increased risk of VTE including systemic lupus erythematosus, Behcet's syndrome, inflammatory bowel disease, rheumatoid arthritis, celiac disease, hyperthyroidism, and systemic vasculitides like granulomatosis with polyangiitis.

Several studies have demonstrated that there may be some similarities in the pathophysiological states between VTE and atherosclerosis, and that they potentially share multiple risk factors. A recent meta-analysis revealed that an association between elevated cholesterol and hypertension and VTE [86]. For instance, a recent meta-analysis has shown VTE to be more common in patients with hypertension than in those without with an odds ratio of 1.40; additionally, total cholesterol and triglycerides were significantly higher in patients with VTE than in those without with a weighted mean difference of 8.94 mg/l and 14 mg/dL, respectively [86]. Smoking is a modifiable risk factor that is associated with an increased risk of VTE, among both men and women. The effect of smoking is thought to be acute as most studies indicate that former smokers have a risk of VTE similar to that of never smokers [87].

The incidence of VTE in pediatric population is lower than that in adults due to physiologic deficiency of coagulation factors leading to reduced capacity to generate thrombin, increased capacity of alpha2-macroglobulin to inhibit thrombin, enhanced antithrombotic potential of the vessel wall, and lack of exposure to acquired thrombotic risk factors [88]. The annual incidence is 0.07–0.14 per 10,000 children, or 5.3 per 10,000 hospital admissions of children, and 24 per 10,000 admissions to neonatal intensive care units [89–92]. Idiopathic VTE in pediatrics is infrequent. At diagnosis, 90% of children with VTE will have ≥2 predisposing factors [90] (Fig. 2).

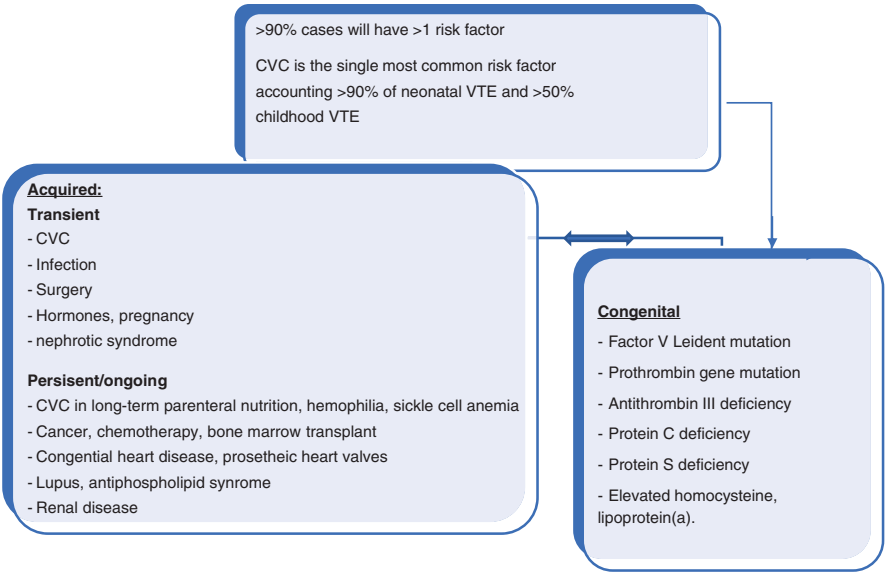

Fig. 2 Risk factors for VTE in pediatrics [90]

Conclusion

The cost of VTE care is rising. Incidence and VTE-related mortality is also increasing. Various acquired and genetic risk factors play a role along with gender, ethnicity in VTE prevalance and mortality. There is heterogeneity in the literature about PE-related mortality. VTE prevention should be the central theme going forward in decreasing VTE related morbidity and mortality.

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PE Diagnosis

Soophia Khan Naydenov and An Thi Nhat Ho

Approach to Patients with Suspected Pulmonary Embolism

Clinical Prediction Rules

Because of the low sensitivity of each individual symptom of pulmonary embolism (PE), the diagnosis is based on the constellation of clinical features. Since 2000, a number of standardized prediction rules have been studied and applied clinically [1–4]. Using a logistic regression analysis of clinical variables, most relevant variables were pulled into the scoring system to predict pretest probability. There are multiple versions of clinical prediction rules for PE, validated simplified and modified versions of them. Most well known are Wells and revised Geneva prediction's rules as given in Table 1 [1, 2, 4, 6, 7]. The proportions of patients with PE were reported to be about 6–13%, 23–35%, and 65–76% in the low, moderate, and high clinical probability, respectively [8].

For patients with a low probability of PE (Wells score < 2), pulmonary embolism rule-out criteria (PERC) rule including the following eight criteria (Table 2) can be used to further categorize patients who could be excluded for PE without further tests [9].

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Table 1 Wells and revised Geneva clinical prediction rule to diagnose PE [7]

Clinical prediction rules					
Wells score			Geneva score		
Components	Original version (points)	Simplified version (points)	Components	Original version (points)	Simplified version (points)
Previous PE or DVT	1.5	1	Previous PE or DVT	3	1
Heart rate > 100	1.5	1	Heart rate 75–94 ≥95	3 5	1 2
Surgery or immobilization within the past 4 weeks	1.5	1	Surgery or fracture within the past month	2	1
Hemoptysis	1	1	Hemoptysis	2	1
Active cancer	1	1	Active cancer	2	1
Clinical sign of DVT[a]	3	1	Unilateral lower limb pain	3	1
Alternative diagnosis less likely than PE	3	1	Pain on lower limb deep venous palpation and unilateral edema	4	1
			Age ≥ 65	1	1
Clinical probability			Clinical probability		
Three-level score			Three-level score		
Low	0–1	N/A	Low	0–3	0–1
Intermediate	2–6	N/A	Intermediate	4–10	2–4
High	≥7	N/A	High	≥11	≥5
Two-level score			Two-level score		
PE unlikely	0–4	0–1	PE unlikely	0–5	0–2
PE likely	≥5	≥2	PE likely	≥6	≥3

[a]*DVT* deep venous thrombosis

Table 2 Pulmonary embolism rule-out criteria

Pulmonary embolism rule-out criteria
Age < 50 years
Heart rate < 100 beats/minute
Oxyhemoglobin saturation > 95%
No hemoptysis
No prior DVT or PE
No unilateral leg swelling
No surgery/trauma requiring hospitalization within the prior 4 weeks
If patients with a low pretest probability of PE fulfill all eight criteria, they do not need further testing

D-Dimer

D-dimer is a fibrin degradation product from the fibrinolysis of a blood clot. D-dimer is highly sensitive but not specific in PE (sensitivity 99%, specificity 41% using the cut-off of 500 micrograms/L) [10] because it could be elevated in other conditions such as malignancy, renal insufficiency, sickle cell disease, and recent surgery [11–13]. D-dimer is used in conjunction with the clinical prediction rule. For patients with unlikely PE by clinical prediction rule (such as Wells score ≤4), a normal D-Dimer level can exclude PE with a negative predictive value up to 99% [8]. Nevertheless, the value of normal D-Dimer in population with high pretest probability for PE is not well elucidated with current studies.

Normal D-dimer levels can increase with age [14]. A proposed age-adjusted D-dimer cut-off has been increasingly studied recently and was associated with a larger number of patients in whom PE could be ruled out safely in combination with an unlikely clinical probability [15].

Adjusted D-dimer level cut off (ng/ml) = age (if over 50 years) x10.

Clinical Use of Prediction Scores and Drawbacks

The original and simplified Geneva and Wells prediction rules are used in combination with D-dimer to rule out PE. The negative predictive value (NPV) of "unlikely PE" by clinical prediction score together with a negative D-Dimer was up to 96–99% in both the emergency and primary care settings [2, 4, 8]. Wells score is slightly more accurate in predicting PE in suspected patients than the revised Geneva score based on a recent meta-analysis [16]. In this study, based on the data from one study, the area under the curve (AUC) of Wells score was 0.778 (sensitivity 63.8–79.3%), which is higher than the AUC of revised Geneva score (0.693, with a sensitivity of 55.3–73.6%).

Hospitalized and critically ill patients are populations in which these clinical prediction rules are not well validated and may not be reliable to either rule in or rule out PE, irrespective of their age [3]. In pregnant and postpartum population, both Wells score and revised Geneva also have a limited value with a low sensitivity and specificity (40–60%, 80% respectively) in diagnosing PE [17].

Imaging Studies

Chest Radiograph (CXR)

Most of the patients with PE have an abnormal chest X-ray. In reviewing all the chest radiographs of 1063 patients with suspected PE in the PIOPED study and

Table 3 Signs of PE in chest X-ray [18, 20]

	Sensitivity	Specificity	Positive-predictive value	Negative-predictive value
Westermark sign	14	92	38	76
Hampton hump	22	82	28	76
Non-specific:				
Pleural effusion	36	70	28	76
Elevated diaphragm	20	85	30	76
Vascular distribution	10	87	21	74

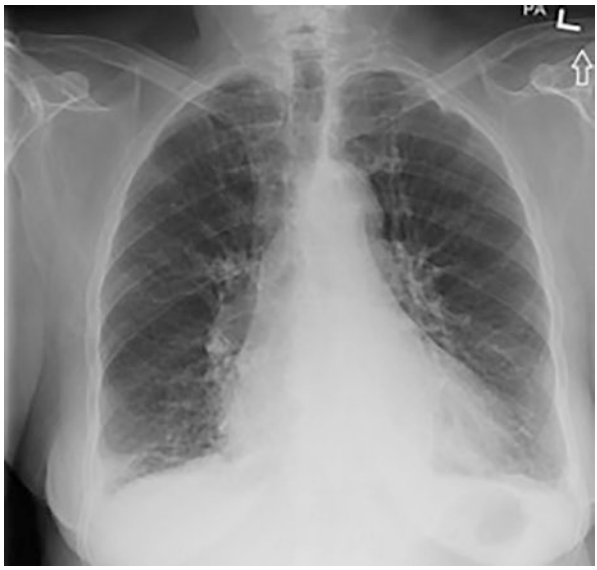

Fig. 1 Chest X-ray showing small bilateral pleural effusions with associated underlying atelectasis and/or airspace disease

2454 consecutive PE patients from the International Cooperative Pulmonary Embolism Registry (ICOPER), abnormal chest X-ray accounts for 63% to 88% of patients [18, 19]. Table 3 lists the clinical diagnostic values of the findings on the chest radiograph. Abnormal signs in CXR (see (Figs. 1 and 2)):

Other non-specific signs in CXR such as atelectasis, prominent central pulmonary artery (the Fleischner sign), and enlarged hilum were also found in acute PE [18].

Cardiomegaly and pleural effusion are the most common chest radiographic abnormality associated with acute PE. Regardless, neither of these findings is sensitive or specific enough to rule in or rule out PE diagnosis, but CXR is still useful in excluding other differential diseases such as pneumonia, pulmonary edema, or pneumothorax [18].

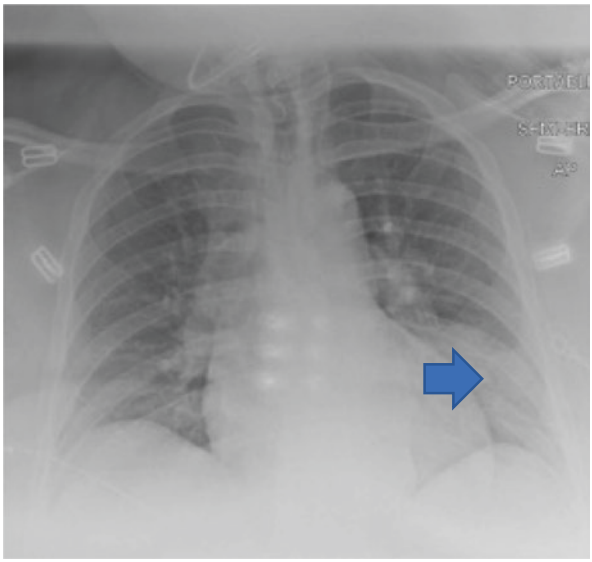

Fig. 2 There is a left lower lobe consolidation(arrow), which is consistent with known pulmonary infarction seen on the patient's prior CT chest. There is no pleural effusion or pneumothorax. The cardiomediastinal silhouette is normal. Intact visible bony thorax

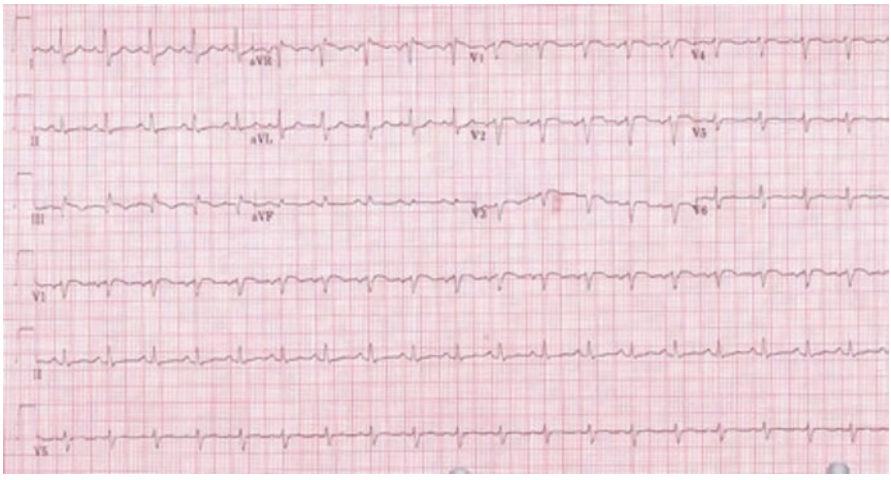

Fig. 3 EKG in a patient with bilateral main pulmonary artery embolisms showing S1Q3T3

Electrocardiogram

Electrocardiogram findings in PE are not specific. The most common findings are tachycardia but bradycardia could also be found in patients with massive PE. Other findings are right bundle branch block, atrial arrhythmia, S1Q3T3 pattern (negative S wave in lead I, Q wave, and inverted T wave in lead III) (Fig. 3) [21].

Table 4 Echocardiography features in pulmonary embolism

Features	Echocardiogram measurements
RV hypokinesis	Decreased S′ tissue Doppler [22] Visual evaluation Decreased fractional area change <30%
RV dilation (without RV wall hypertrophy)	RV > LV at the base or RV > 4 cm at the base in the 4-chamber view (Fig. 4)
Tricuspid regurgitation	TR velocity >2.7 m/sec [23]
Detection of thrombi in the right heart and major pulmonary arteries	
RV afterload stress[b]	A plus 2B: A: Dilation of RV (Fig. 5) B criteria: (1) TR jet velocity >2.8 m/s, or (2) >2.5 m/s (absence of inspiratory collapse of IVC), (3) dilation of Right pulmonary artery (>12 mm/m^2 body surface area) on the parasternal view, (4) RV wall thickness >5 mm, (5) loss of inspiratory collapse of IVC [24][a] OR Interventricular septum flattening in systol [25]
"60/60 sign"	Pulmonary artery acceleration time <60 ms in the presence of TR pressure gradient <60
McConnell sign	Normokinesia and/or hyperkinesia of the apical segment of the RV free wall despite hypokinesia and/or akinesia of the remaining parts of RV free walls

[a]83% of patients with suspected PE and RV afterload stress fulfilling these criteria have PE on CTA [24]
[b]Chronic RV stress when either RV wall thickness >5 mm or TR jet velocity >3.7 m/s

Echocardiography

Echocardiography findings in acute PE are listed in Table 4:

See Table 5 for diagnostic values of RV pressure overload, 60/60 sign, and McConnel signs in patients with or without known previous cardiorespiratory diseases (Table 6).

McConnell's sign is not proven to be very specific for the PE diagnosis either. In a study by Vaid et al., in a group of 73 patients who had findings of McConnell's sign on Echo and had undergone another diagnostic study for VTE, only 57% of patients were confirmed to have VTE.

None of the echocardiogram findings or combinations of them are sensitive or specific enough to rule in or rule out the diagnosis of acute PE. Especially in patients with known previous cardiorespiratory diseases, acute PE only presents in 21% of the patients with RV pressure overload criteria.

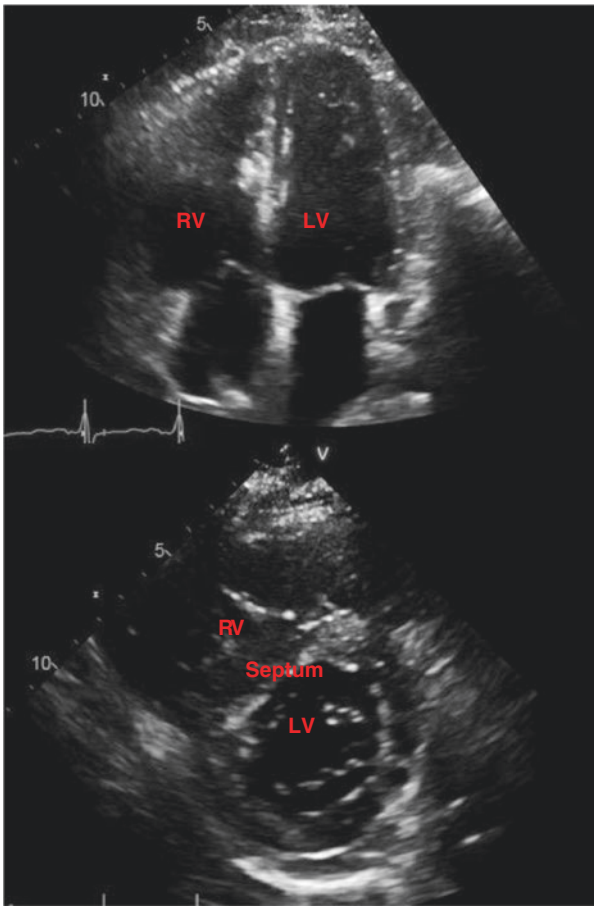

Fig. 4 Transthoracic echocardiogram showing moderately enlarged right ventricle (RV) size and D-shaped Left ventricle (LV)

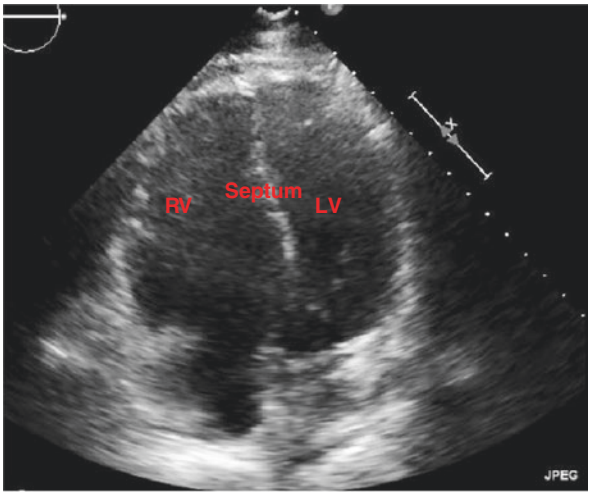

Fig. 5 Right ventricular dilatation. Bowing of the interventricular septum into the left ventricle (LV) indicating higher right ventricular (RV) pressure

Table 5 Diagnostic value of echocardiographic signs suggesting the presence of acute PE in subgroups with and without known previous cardiorespiratory disease [26]

	Patients without known previous cardiorespiratory diseases			Patients with known previous cardiorespiratory diseases		
	RV pressure overload criteria	60/60 sign	McConnell sign	RV pressure overload criteria	60/60 sign	McConnell sign
Specificity (%)	78	100	100	21	89	100
Sensitivity (%)	81	25	19	80	26	20
Positive predictive value (%)	90	100	100	65	82	100
Negative predictive value (%)	64	37	35	36	40	40

Computed Tomography Pulmonary Angiography (CTA)

CT pulmonary angiography allows visualization of the pulmonary emboli, with the advantage of detecting other pulmonary causes for the clinical symptoms of the patients. The predictive value of CTA varied significantly depending on the clinical assessment and the location of the pulmonary emboli. In the PIOPED II trial, the negative-predictive value for CTA in patients with high clinical probability was only 60%, while the positive-predictive value was only 58% in patients with low clinical probability [27]. The authors recommended additional testing when the clinical probability was inconsistent with the imaging results. Diagnosis accuracy decreased substantially with subsegmental arteries. CTA has 97% positive predictive value (PPV) in the main or lobar artery clot but only 25% in the subsegmental branch [27]. Images of subsegmental arteries were non-diagnostic in up to 55% branches with poor interobserver agreements. Clinical significance of subsegmental PE is suggested to be low based on a recent meta-analysis because although it was detected almost double by multiple-detector CTA compared to CTA, the 3 month thromboembolic risk was low and similar in both groups (0.9% vs 1.1%) [28].

In patients with a high pretest probability of PE, CTA could miss a substantial percentage of patients with PE, even with the combination of negative D-dimer. In a recent study of 257 patients with Wells score of >6, 130 patients had negative CTA and 16 of those patients (12.5%) were found to have PE [29].

Additionally, CTA may be utilized for risk stratification to estimate the severity of PE. Such features include right ventricular-to-left ventricular (RV/LV) diameter ratio >1, flattening of interventricular septum or septal bowing, reflux of contrast material into the IVC and hepatic veins. In the observational study of 56 patients with acute PE by Park et al., the odds ratio (OR) of adverse outcomes for RV/LV ratio >1, septal bowing, and proximal PE was 19.2 [32]. The similar OR for RV hypokinesia was 13.4. All the above features were associated with RV hypokinesia on echocardiography. The authors concluded that rapid risk stratification of patients with acute PE based on chest CT could be compared with echocardiography [32].

Table 6 Reported diagnostic accuracy of CTA in PE diagnosis

Reference	Number of patients	Pretest probability	PE prevalence (%)	Sensitivity (%)	Specificity (%)	Inconclusive (%)	False negative
[30]	149	Not reported	45	82–94	93–96	Not reported	Isolated subsegmental PE
[31]	110	Not reported	23	92	96	Not reported	
[27]	824	Suspected, all low, moderate, high	23	83	96	6	

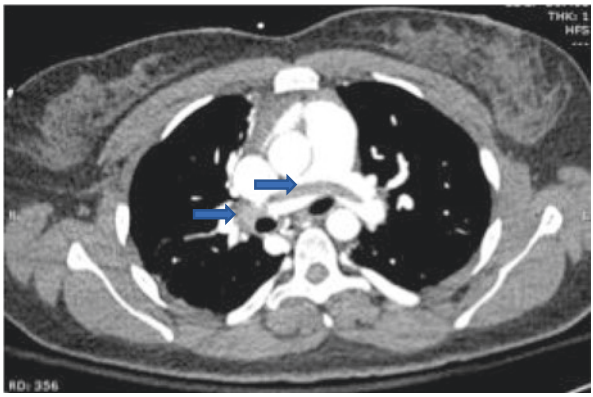

Fig. 6 CTA showing the large filling defect (saddle embolus) in the main pulmonary artery at its bifurcation into the right and left pulmonary arteries

CTA has several disadvantages: radiation exposure, inability to perform in kidney failure patients due to contrast-induced nephropathy risks, inconclusive of imaging due to artifacts, and non-diagnostic sub-segmental arteries are the limitations of CTA. A minimum radiation dose of 2.0 rad (20 mGy) of a single CT pulmonary angiography to the breasts, which is higher than the radiation exposure dose of <0.300 (3mGY) of a standard two-view mammography is recommended by the American College of Radiology [33]. In a study to measure the organ and effective radiation dose of 64-detector CT, the relative risk for breast cancer incidence was 1.004–1.042, while lung cancer risk was 1.005–1.076 for a single examination. However, when taking into account the mortality risk of untreated PE, the benefit-to-risk ratio of CTA remained substantially high [34].

Over the past two decades, the rapid development of CT scan has reduced the limitations and the inconclusive images. Single-detector CT has been increasingly replaced by multidetector CT (higher volume coverage in one rotation time) and the improvement of contrast agent injection protocols. This leads to a decrease in the acquisition time of the entire chest [35], thus lowering the radiation dose, reducing patients' motion artifacts, and decreasing inconclusive scans from 10% to 2% [36].

(i) Diagnostic Criteria

1. For acute PE based on CTA, include the following [37]:
   - Arterial occlusion with failure to enhance the entire lumen due to a large filling defect with an enlarged artery (Fig. 6).
   - A partial filling defect surrounded by contrast ("polo mint" sign and "railway track" sign) (Fig. 7).
   - Acute angle was formed between the intraluminal filling defect and the arterial wall.
2. Diagnostic criteria for chronic PE include [37] the following:
   - Complete occlusion of a vessel which is smaller than adjacent patent vessels

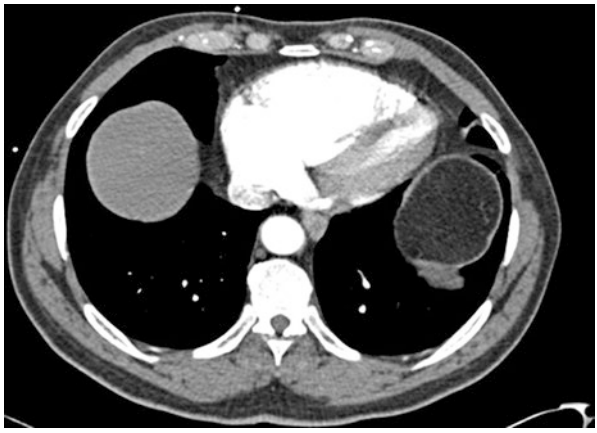

Fig. 7 CTA showing flattening and bowing of the interventricular septum and dilated right ventricle (RV) compared to the left ventricle (LV) concerning for right heart strain in a patient with PE

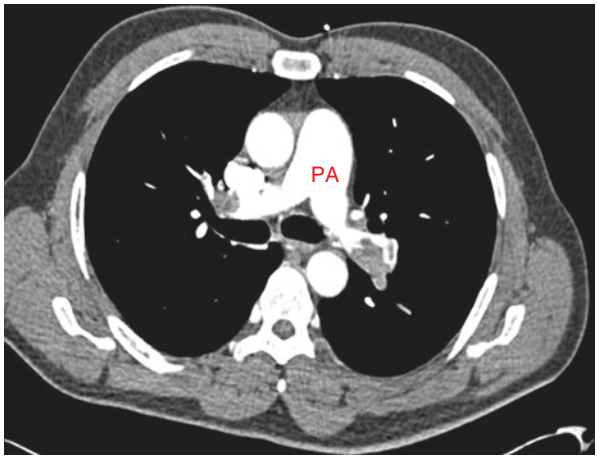

Fig. 8 CTA showing large filling defects in the distal aspects of the right and left main pulmonary arteries consistent with bilateral acute pulmonary emboli. Mild dilatation of the main pulmonary artery

- Peripheral, crescent-shaped intraluminal defect that forms obtuse angles with the vessel wall (Fig. 8)
- Contrast material flowing through thickened, smaller arteries
- Web or flap within a contrast material-filled artery
- Collateral vessels and accompanying mosaic perfusion pattern, or calcification within eccentric vessel thickening. (Fig. 9)

Pulmonary Angiography

Traditionally, it used to be the "gold standard" for diagnosing PE; pulmonary angiography has been replaced with the use of CTA. Angiography could still be considered in patients with high pretest probability but indeterminate results by non-invasive

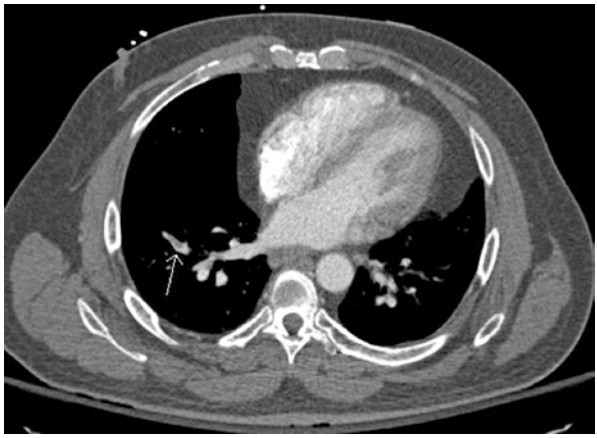

Fig. 9 Segmental PE

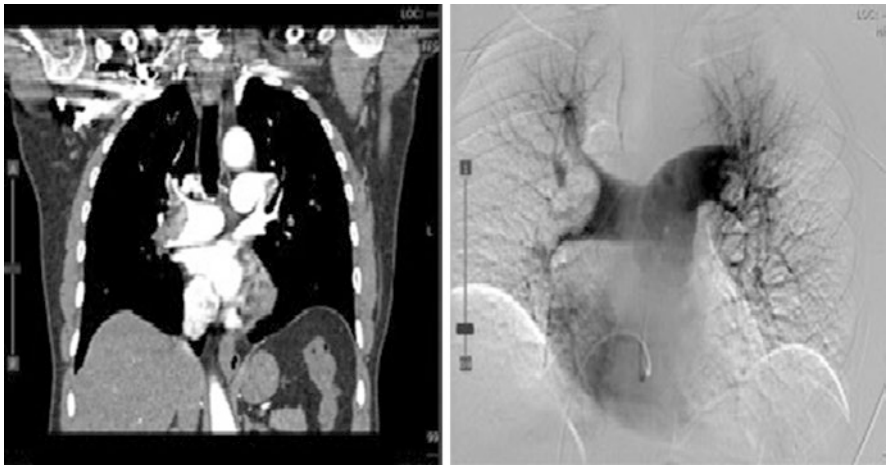

Fig. 10 Filling defect on the right main pulmonary artery (right panel) in catheter-based pulmonary angiography and CT angiogram on the same patient (left panel)

studies if clinically indicated. Angiography nowadays is mostly used in the setting of interventional procedures for clot removal or lysis. (Fig. 10).

Ventilation-Perfusion (V/Q) Scan

V/Q scan is a commonly used imaging study to diagnose PE. A mismatched ventilation defect indicates PE. In the perfusion phase, ^{99m}Tc-labelled macroaggregated human albumin is injected to the patients which gets disseminated to the pulmonary capillaries, enabling scintigraphic assessment of lung perfusion. The ventilation phase

uses multiple inhaled tracers, such as ^{99m}Tc aerosols/carbon microparticles to assess ventilation [7]. Based on the PIOPED study, V/Q scan is reported as either normal, low, intermediate, or high probability for PE. Two large prospective clinical trials, PIOPED and PISA-PED trials, showed that normal V/Q scans are highly accurate to exclude PE, even in patients with high pretest probability for PE and this finding had been consistent in all subsequent studies [38]. The sensitivity of V/Q scan in the PIOPED trial was 41% with a specificity of 97%. PPV of high-probability, intermediate-probability, and low-probability scans are 88%, 33% and 12%, respectively [39]. See Fig. 11 for example of multiple segmental PE on V/Q scan.

The main limitation of planar V/Q scintigraphy is that a large percentage of scans fall into the category of intermediate probability of PE. Single photon emission computed tomography (SPECT) V/Q scan is a nuclear scan with a three-dimensional image construction and may overcome the limitations of the planar V/Q scan [36]. The SPECT V/Q has higher sensitivity and specificity than planar V/Q even in the presence of comorbid diseases, such as COPD or pneumonia [40, 41].

Since the introduction of hybrid SPECT/CT tomography, a low-dose CT scan (non-contrast) can be performed immediately before the SPECT V/Q scan with a total acquisition time of less than 15 minutes [42]. The SPECT V/Q/CT low dose has less radiation dose than CTA with a dose of 0.9–1 mSv [43]. This study could be done in patients who are indeterminant for PE by planar V/Q scan or in those who cannot receive a high dose of radiation exposure and iodine contrast exposure [36, 44]. The SPECT V/Q /CT has increased specificity of SPECT V/Q from 88% to 100% without affecting the sensitivity (97%) [45]; however, data also reported an overdiagnosis rate [46]. More studies on the diagnostic value of SPECT V/Q/CT low dose still need to be done.

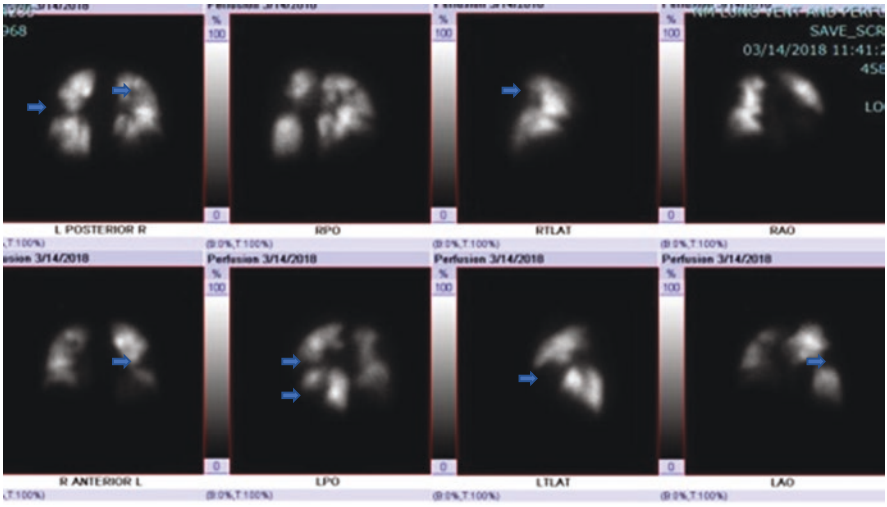

Fig. 11 Multiple segmental PE on V/Q scan– perfusion images (blue arrows: the perfusion defects in multiple segments bilaterally)

Ultrasonography

(i) Compression Venous Ultrasonography

Deep venous thrombosis (DVT) is found in 30%–50% of patients with proven PE [6, 47, 48]. Negative DVT cannot exclude PE. The sensitivity and specificity of compressive venous ultrasonography to diagnose DVT were 39% and 99%, respectively [49].

(ii) Lung Ultrasound

Lung ultrasound signs of PE include peripheral parenchymal consolidations due to embolic vascular occlusion or wedge-shaped, triangular, or rounded pleura-based hypoechoic lesions with a central hyperechoic bronchiolar pattern, with or without pleural effusion.

The pleural-based, wedge-shaped hypoechoic lesions have a sensitivity of 90% and specificity of 60% in diagnosing PE [50]. A recent systematic review of accuracy test studies of lung US for the diagnosis of PE in patients with clinical suspicion of PE showed a sensitivity of 87% and specificity of 82%. Limitations include inaccessible lung areas, especially central lesions, or when "early infarction" disappears after PE's occurrence [51].

(iii) Triple Point-of-Care Ultrasound (POCUS)

Triple POCUS includes lung, heart, and leg veins ultrasound. In the study of 357 patients by Nazerian et al., the patients with Wells score >4 or positive D-Dimer, one or more of the following findings: subpleural infarcts, right ventricular dilatation, or DVT reached a sensitivity of 90% and specificity of 86% of diagnosing PE (Table 7).

Table 7 Accuracy of lung, heart, veins, and multiorgan ultrasonography for the diagnosis of PE [52]

Ultrasonography	Sens % (95% CI)	Spec % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	+LR (95% CI)	−LR (95% CI)
Lung	60.9 (51.1–70.1)	95.9 (92.7–98)	87 (77.4–93.6)	84.6 (79.9–88.7)	15 (8–28.1)	0.4 (0.3–0.5)
Heart[a]	32.7 (24.1–42.3)	90.9 (86.6–94.2)	62.1 (48.4–74.5)	74.8 (69.5–79.7)	3.6 (2.2–5.8)	0.7 (0.6–0.8)
Vein	52.7 (43–62.3)	97.6 (94.8–99.1)	90.6 (80.7–96.5)	82.2 (77.4–86.4)	21.7 (9.7–48.8)	0.5 (0.4–0.6)
Multiorgan	90 (82.8–94.9)	86.2 (81.3–90.3)	74.4 (66.1–81.6)	95.1 (91.4–97.5)	6.5 (4.8–8.9)	0.12 (0.07–0.2)
Negative multiorgan plus alternative diagnosis	100 (96.7–100)	42.9 (36.7–49.3)	43.8 (37.6–50.2)	100 (96.5–100)	1.75 (1.6–1.9)	0

Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiogram (MRA)

MRI also plays an important role in detecting PE. Thanks to recent advances in acquisition technology, MRI's acquisition time and volumetric coverage have significantly improved [5]. Non-contrast and contrast-enhanced MRI are both available, but there is less evidence of the use of non-contrast MRI in the routine clinical MRA. Contrast-enhanced MRI commonly uses gadolinium-based contrast to enhance pulmonary arteries. Dynamic contrast-enhanced MRI can be used to detect lung perfusion defects, similar to that of V/Q scan by rapid volumetric imaging sequence after gadolinium administration. Non-contrast techniques can be used as well but are limited to the evaluation of only central or lobar pulmonary arteries [53]. See (Fig. 12) for a PE MRI.

Pulmonary MRA has a sensitivity of 55% and specificity of 99% when compared to CTA in the acute setting in a study of 23 patients by Hochhegger et al. in 2011

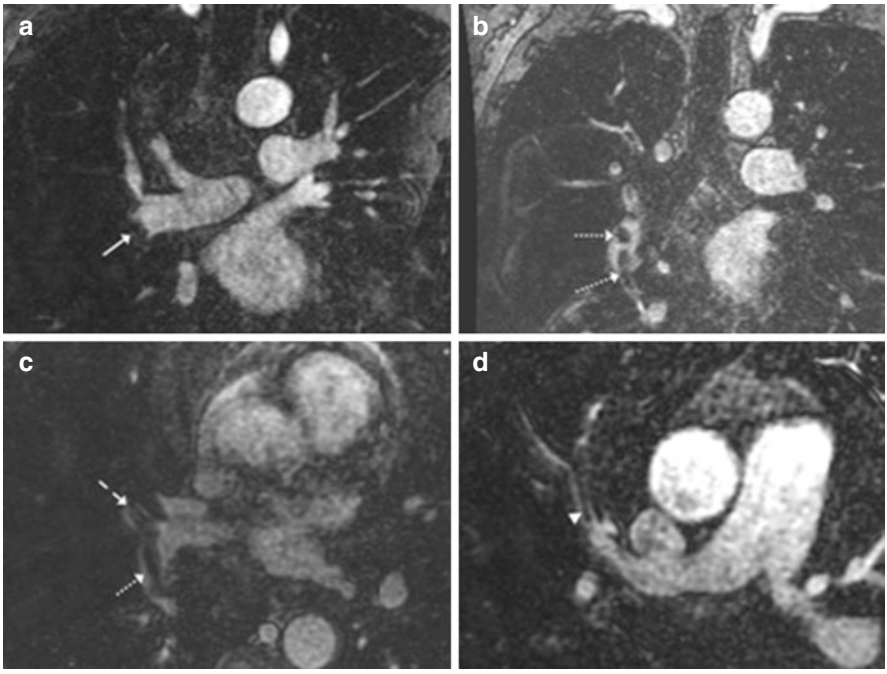

Fig. 12 Low-signal-intensity filling defects (arrows and arrowheads) are the most common appearance of pulmonary embolism on MRA. In these four patients with PE identified on MRA, filling defects are present in (**a**) the right lower lobe (arrow); (**b**) the right middle lobe (dashed arrows); (**c**) right middle (dashed arrow) and lower (dotted arrow) lobes; and (**d**) anterior right upper lobe (arrowhead). (We sincerely thank Dr. Christopher J. Francois, Dr. Donald Benson, Dr. Mark Schiebler, Dr. Scott Nagle for the permission to use their published MRI images [5])

[53]. In a more recent study in a larger sample of 93 patients in 2017 by Pasin et al., the sensitivity of MRI was 85%, with a specificity of 99% compared to CTA. More research is still needed with regard to the diagnostic accuracy of MRI in the detection of PE in light of robust technical improvements nowadays.

Clinically, MRI may be utilized in patients with contraindications to iodinated contrast, young female, or pregnant patients. MRI can also be used if intravenous access is limited because contrast can be injected through a pump at a lower injection rate. However, patients who are unstable or unable to maintain a breath-hold are not recommended for pulmonary MRA.

Conclusion

PE diagnosis requires comprehensive consideration of clinical pretest probability and the understanding of diagnostic imaging modalities. In general, the use of clinical prediction scores, D-dimer test, echocardiogram, Doppler ultrasound of lower extremities, bedside ultrasound, CTA, and VQ scan still remain the most prevalent and helpful diagnostic modalities for patients with suspected PE with multiple studies validating their diagnostic values. More recent developments of MRI, SPECT V/Q scan, and CT/VQ SPECT bring more promises in this field in terms of improving the diagnostic accuracy. Physicians should understand the advantages and drawbacks of these diagnostic studies in order to give an accurate diagnosis and prognosis for patients with suspected acute PE.

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Risk Stratification of Acute PE

Gabrielle VanSpeybroeck and Belinda Rivera-Lebron

Introduction

In recent years, venous thromboembolism (VTE) has been increasingly recognized as a major public health concern. The Centers for Disease Control and Prevention outlines that up to 300,000–600,000 individuals are affected yearly in the United States with acute pulmonary embolism (PE) and 60,000–100,000 Americans die each year as a result of PE [1].

Classification of Acute PE

PE can present in a variety of ways, ranging from asymptomatic and incidentally identified, to life-threatening or even sudden death. Clinical classification of acute PE is primarily based on the ability of the right ventricle (RV) to overcome the thrombus burden. After acute PE has been diagnosed, classification and risk stratification are necessary to determine prognosis and appropriate therapy.

The American Heart Association (AHA) guidelines classify PE into three groups: massive, submassive, and non-massive or low-risk PE [2] (Table 1). Massive PE is defined as acute PE with sustained hypotension (systolic blood pressure (SBP) <90 mm Hg for at least 15 minutes or requiring ionotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular (LV) dysfunction), pulselessness, or persistent profound bradycardia (heart rate (HR) <40 bpm with signs or symptoms of shock). Submassive PE is an acute PE without systemic hypotension (SBP ≥ 90 mm Hg) but with either RV dysfunction

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Table 1 The American Heart Association (AHA) [2] and the European Society of Cardiology (ESC) [3] Classification and Prognostic Risk Stratification of Acute Pulmonary Embolism

	Mortality Risk	Shock or Hypotension	RV Dysfunction	Cardiac Biomarkers	PESI Class III-V or sPESI ≥1
ESC	High	+	+	+[a]	+[a]
	Intermediate-high	–	+	+	+
	Intermediate-low	–	Either one (or none) positive		+
	Low	–	–[b]		–[b]
AHA	Massive	+			
	Submassive	–	Either one positive		
	Low or non-massive	–	–		

ESC European Society of Cardiology, *AHA* American Heart Association, *RV* right ventricle, *PESI* pulmonary embolism severity index, *sPESI* simplified pulmonary embolism severity index

[a]Per ESC, neither cardiac biomarkers or PESI calculation are necessary in the setting of acute PE with hypotension

[b]Per ESC, in low-risk PE, assessment of RV dysfunction and cardiac biomarkers are optional; if assessed, both negative

or myocardial necrosis. RV dysfunction is defined as the presence of at least one of the following: RV dilation (RV/LV diameter ratio >0.9) or RV systolic dysfunction on echocardiography; RV dilation (RV/LV diameter ratio >0.9) on contrast-enhanced chest computed tomography angiography (CTA); elevation of brain natriuretic peptide (BNP) (>90 pg/mL); elevation of N-terminal pro-BNP (NT-proBNP) (>500 pg/mL); or electrocardiographic changes (new complete or incomplete right bundle branch block, anteroseptal ST elevations or depression, or anteroseptal T-wave inversion). Myocardial necrosis is defined as either of the following: elevation of troponin I (>0.4 ng/mL); or elevation of troponin T (>0.1 ng/mL). Low-risk PE is an acute PE with the absence of clinical markers of adverse prognosis that define massive or submassive PE as outlined above, therefore are normotensive, have normal biomarker levels, and no RV dysfunction on imaging.

The European Society of Cardiology (ESC) classification of acute PE differs slightly in nomenclature and has integrated prognostic factors [3] (Table 1). The classification is primarily based on the estimated PE-related early mortality risk. Patients that are hemodynamically unstable with shock or hypotension are identified as high-risk PE. For those without signs of shock or hypotension, the ESC guidelines recommend the use of three risk parameters to further classify patients: risk scoring system (Pulmonary Embolism Severity Index (PESI) or simplified PESI (sPESI)) (Table 2), RV imaging (with CTA or echocardiogram), and cardiac laboratory markers. The PESI and the sPESI represent a validated clinical scoring system that predicts 30-day mortality (see next section on Clinical Scoring Systems for more details) [4, 5]. Intermediate-risk PE patients have a PESI class III–V or sPESI ≥1, and/or RV dilation or dysfunction on imaging, and/or the presence of positive biomarkers suggestive of myocardial injury (troponin) or

Table 2 Original and Simplified Pulmonary Embolism Score Index Scores [4, 5]

Parameter	Original version (PESI)	Simplified version (sPESI)
Age	Age in years	+1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	+1 point
Chronic heart failure	+10 points	+1 point
Chronic pulmonary disease	+10 points	+1 point
Pulse rate ≥110 b.p.m	+20 points	+1 point
Systolic blood pressure <100 mm Hg	+30 points	+1 point
Respiratory rate > 30 breaths per minute	+20 points	–
Temperature <36 deg. C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhemoglobin saturation <90%	+20 points	+1 point
30-day mortality risk (%)	*Class I*: ≤65 points Very low (0–1.6%) *Class II*: 66–85 points Low (1.7–3.5%) *Class III*: 86–105 points Moderate (3.2–7.1%) *Class IV*: 106–125 points High (4.0–11.4%) *Class V*: >125 points Very high (10.0–24.5%)	*0 points* (1.0%) *≥1 point(s)* (10.9%)

myocardial distention (BNP or NT-proBNP). Intermediate-risk PE is further subclassified into intermediate-high risk (presence of both RV dysfunction on imaging and biomarker elevation) or intermediate-low risk (either RV dysfunction or biomarker elevation). Those with PESI class I or II, or sPESI 0, normal RV function by echocardiography or CTA, and normal cardiac biomarkers are classified as low-risk PE patients.

Risk Stratification of Acute PE

Clinical Scoring Systems

The Pulmonary Embolism Severity Index or PESI score is the most validated clinical prediction rule for acute PE [4]. The PESI score was developed to help prognosticate patients and may be used to guide the intensity of treatment in acute PE. Eleven PE risk factors classify patients into classes ranging from I to V (Table 2). Higher scores indicate a higher mortality risk. The PESI score has been shown to correlate with 30- and 90-day mortality [6]. Specifically, class I and class II patients confer a very low (30-day mortality 0–1.6%) and low (1.7–3.5%) mortality; class III has a moderate (3.2–7.1%) mortality; and class IV and V have a high (4–11.4%) and very high (10–24.5%) mortality risk at 30 days [4].

The PESI score has been adjusted into a simplified PESI score, or sPESI, which has a similar prognostic accuracy and is easier to use than the original [5]. sPESI includes seven risk factors (Table 2).

PESI and sPESI can be immensely helpful clinically, particularly in identifying patients with low-risk PE (PESI classes I–II or sPESI 0) who may be considered for outpatient PE management [7].

The Bova score is another grading system for stratifying the risk of short-term complications in normotensive PE patients [8, 9]. The score consists of four variables: tachycardia, hypotension, elevated troponin, and RV dysfunction, and its goal is to identify intermediate-risk patients. Bova score 0–2 corresponds to stage I – low risk (4.4% PE-related complications and 3.1% PE-related mortality); Bova score 3–4 corresponds to stage II – intermediate risk (18% PE-related complications and 6.8% PE-related mortality); and Bova score >4 corresponds to stage III – high risk (42% PE-related complications and 10% PE-related mortality). A modified Bova score was validated in hemodynamically unstable patients and is highly effective in predicting poor outcome in acute PE [10].

Biomarkers

Troponin

Troponin elevation can be seen in the setting of micro-infarction after myocardial damage. Elevated cardiac troponin has high sensitivity and specificity for myocardial damage [11] and may be present in patients with intermediate- or high-risk PE. A hypothesized mechanism for troponin elevation in acute PE has been compression of the right coronary artery as a result of RV strain and tension, and subsequent myocardial injury [12].

Elevated troponin I or T is associated with adverse prognosis and high mortality in hemodynamically stable patients [13, 14]. In a large meta-analysis of normotensive patients with acute PE, there was an associated 4.26-fold increased overall mortality at short-term follow-up in those patients with elevated troponin (odds ratio (OR) 4.26, 95%CI 2.13–8.5, $p = 0.125$) [14]. In addition, troponin elevation has been associated with worse short-term hospital outcomes in hemodynamically unstable patients presenting with acute PE [15].

While troponin elevation helps with prognostication of intermediate-risk or submassive PE, normal levels may help identify those with intermediate-low- or low-risk PE. Normal troponin has a high negative predictive value and may be a good tool to identify patients that may be treated with anticoagulation alone and those patients who may be appropriate for outpatient management [16].

B-Type Natriuretic Peptide

The B-type natriuretic peptide, or BNP, is released in response to shear stress on the myocytes and myocardial stretch from increased RV overload that precedes RV dysfunction. NT-proBNP is the biologically inactive form of BNP. BNP and NT-proBNP elevations are associated with RV dysfunction in acute PE and with increased mortality and adverse outcomes at short-term follow-up [17–19]. A large systematic review and meta-analysis found that the overall OR for death was 7.6 (95%CI 3.4–17) and for in-hospital adverse events was 6.8 (95%CI 4.4–10) in patients presenting with elevated BNP [17].

It is important to consider that BNP elevation has low specificity and low negative predictive value, and can also be elevated in a variety of cardiopulmonary conditions, such as congestive heart failure. However, in the presence of a known PE, a normal BNP or NT-proBNP may help stratify patients with intermediate-low- or low-risk PE.

There is no recommendation on whether BNP or NT-proBNP should be preferred for the risk stratification of acute PE.

Right Ventricular Imaging

Echocardiogram

The ability to visualize the RV in real time with an echocardiogram is used to risk stratify acute PE. Twenty-five percent or more of the pulmonary vasculature needs to be obstructed with thrombus in order for the RV to be affected [20].

Transthoracic echocardiogram (TTE) provides an assessment of RV structure and function. Presence of RV dilation, increased RV/LV diameter ratio, interventricular septal compression, paradoxical septal motion, and RV hypokinesis may be identified in acute PE and indicate right heart dysfunction or RV strain. McConnell's sign, which refers to a regional pattern of RV free wall dysfunction with sparing of the apex, has also been described with acute PE [21]. All these measures have been identified as predictors of worse outcomes and increased risk of death, particularly in patients who are normotensive on presentation [22–25]. Tricuspid annulus plane systolic excursion (TAPSE) as a measure of dysfunction at the tricuspid valve has also been associated with poor outcomes in the setting of acute PE [26].

While some studies have evaluated these echocardiographic findings with prognosis in acute PE, there is not one uniform definition of RV dysfunction or RV strain by echocardiography, and often it is defined by a combination of these findings [27].

The most commonly studied marker of RV dysfunction is poor RV wall motion. RV hypokinesis has been an independent predictor of 30-day mortality as evidenced by a hazard ratio (HR) of 1.94 (95%CI 1.23–3.06, $p = 0.005$) in one study [22]. The International Cooperative Pulmonary Embolism Registry (ICOPER) reported that 40% of patients presenting with acute PE had signs of RV hypokinesis [20]. Its presence not only was associated with an increased risk of death (relative risk (RR) 6.0, 95%CI 1.1–111.5) but also was a risk for recurrent PE [24, 28]. The presence of RV strain can help triage patients upon presentation to the hospital for advanced therapies, such as systemic or catheter-directed thrombolysis or thrombectomy. It is important to note that the absence of right heart dysfunction on echocardiography does not rule out the presence of acute PE [29].

Additionally, transthoracic echocardiography may also be considered as a diagnostic tool in patients with high pre-test probability of having an acute PE but with hemodynamic instability or inability to travel for CTA. Other high-risk features identified by echocardiography are the presence of right heart thrombi and/or patent foramen ovale (Fig. 1). ICOPER reported that 4% of patients presented with intracardiac thrombus [20, 30]. These findings have also been associated with an increased risk of death in acute PE.

The utility of transesophageal echocardiography (TEE) in diagnosis of acute PE has been considered as well. The ability to visualize proximal perimural thrombi evident via TEE is a useful feature of this modality, and one that can be beneficial in identification of patients with acute PE. Sensitivity of TEE in identification of acute PE in patients with signs of RV overload has been reported 80% and specificity at 97%, highlighting possible value in acute PE diagnosis and special utility in visualization of even proximal clots visualized at the bedside [31].

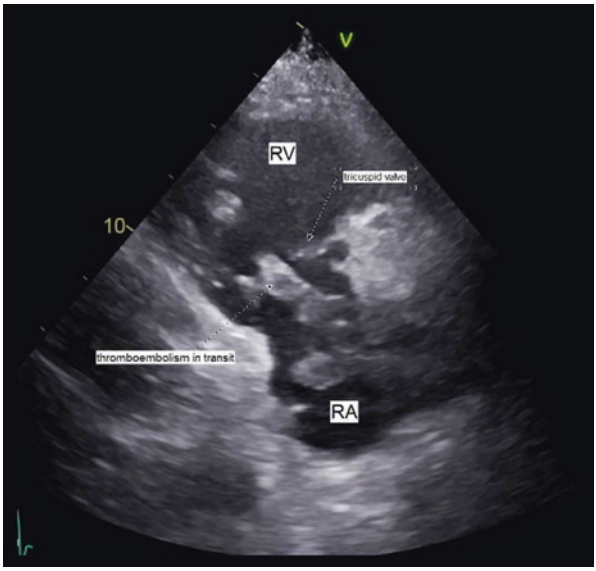

Fig. 1 Pulmonary embolism in transit as noted on transthoracic echocardiography. Right ventricle (RV) and right atrium (RA) labeled. Tricuspid valve and mobile thromboembolism marked with arrows. (Courtesy of the University of Pittsburgh Medical Center, Department of Echocardiography)

As an alternative to formal echocardiography, bedside point-of-care ultrasound can sometimes be the quickest way to evaluate the RV. It may be considered in hemodynamically stable patients to assess for RV strain and for hemodynamically unstable patients unable to travel to radiology for CTA [23]. Bedside focused cardiac ultrasound has been less studied than other echocardiographic modalities, but in one study, it was found to have a likelihood ratio of 7.03 (95%CI 4.01–10.99) in diagnosing right heart dysfunction associated with acute PE [32].

Computed Tomographic Angiography (CTA)

Contrast-enhanced chest computed tomography angiography (CTA) is the gold standard for the diagnosis of PE due to its sensitivity and specificity profile, as well as its wide availability across hospitals. As the resolution of CTA improves, distal portions of pulmonary vasculature are better defined and small, subsegmental emboli can be identified.

The embolic burden on CTA has not been shown to be associated with short-term death due to PE [33]. Greater clot volume, however, has been shown to be associated with a higher incidence of right heart dilatation [34].

CTA, in addition to confirming the diagnosis of PE, may provide risk stratification, by providing RV size [35]. Increased RV/LV diameter ratio on CTA has been shown to be associated with higher short-term mortality, with an OR for mortality in one study reaching 8.64 (p-value <0.0015) [36, 37]. RV/LV diameter ratio is estimated using the standard axial view, measuring the maximum distance from the interventricular septum to the endocardial border perpendicular to the long axis of the heart (Fig. 2). Ventricular septal bowing may also indicate the presence of RV dysfunction and is demonstrated by deviation of the septum (Fig. 3). Ventricular

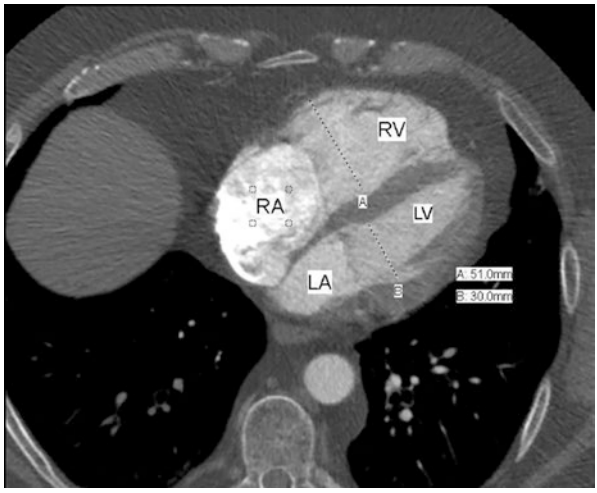

Fig. 2 Measurement of ventricular dimensions from axial view on CT angiography (CTA) in a patient with acute pulmonary embolism. Right atrium (RA), left atrium (LA), right ventricle (RV) and left ventricle (LV) marked. Note increased RV/LV ratio marked in dotted lines. (Courtesy of the University of Pittsburgh Medical Center, Department of Radiology)

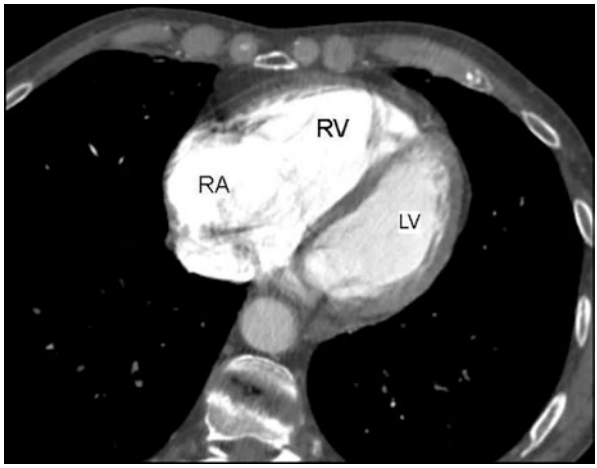

Fig. 3 Ventricular septal bowing in acute PE as noted on CT angiography (CTA). Ventricular septum bows towards the left ventricle (LV). Right atrium (RA) and right ventricle (RV) also identified. (Courtesy of the University of Pittsburgh Medical Center, Department of Radiology)

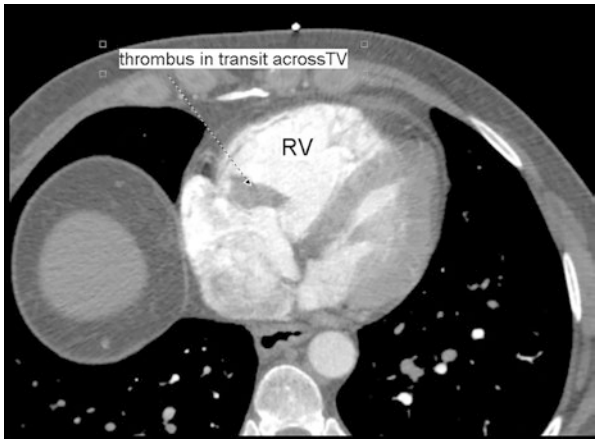

Fig. 4 Right heart thrombi or thrombus-in-transit seen on CT angiography (CTA). Right ventricle (RV) and thrombus in transit across tricuspid valve (TV) identified. (Courtesy of the University of Pittsburgh Medical Center, Department of Radiology)

septal bowing has low sensitivity in predicting death due to PE [33, 38, 39]. Rarely, other findings might be seen using CTA, such as right heart thrombi or thrombus-in-transit (Fig. 4).

Integrated Risk Stratification

While the identification of the above risk factors individually indicates worse prognosis, the combination of multiple parameters integrated into a risk stratification system has been proposed to be superior [40, 41]. However, the best combination in an attempt to provide risk stratification of clinical findings with imaging and laboratory tests to predict an adverse outcome is yet to be identified. Such integrated

systems are helpful in both those who are hemodynamically stable and those with higher risk features who may benefit from advanced interventions [42, 43].

The PROgnosTic valuE of Computed Tomography (PROTECT) study demonstrated that utilizing the sPESI score in addition to BNP elevation has good prognostic value and predicts all-cause mortality at 30 days [41].

A limitation of utilizing an integrated risk stratification system that includes imaging is that not one single imaging finding on echocardiography or CTA has been identified as the most specific display of right heart dysfunction in acute PE.

The best approach is that once acute PE is diagnosed, risk stratification is recommended using a composite of clinical appearance, systolic blood pressure, heart rate, respiratory rate, oxygen requirement, PESI or sPESI, imaging for RV dysfunction (CTA or echocardiography) and biomarkers (troponin, BNP or NT-pro-BNP).

Summary

Acute PE is classified according to the AHA as massive, submassive, and low risk. In contrast, the ESC guidelines utilize integrated prognostic factors and classify PE as high-, intermediate-high-, intermediate-low-, and low-risk PE. Elevated cardiac biomarkers (troponin and BNP) and the presence of RV strain on imaging (CTA or echocardiogram) are associated with worse prognosis. Using prognostic parameters, such as clinical scoring systems, cardiac biomarkers, and imaging may be useful in identifying hemodynamically stable patients at risk of decompensation and who may benefit from advanced therapies.

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Bleeding Risk Considerations Prior to Initiation and Duration of Anticoagulation Therapy for the Treatment of Venous Thromboembolism

John R. Bartholomew

Introduction

Bleeding during anticoagulation therapy is common and can be serious. It can result in significant morbidity and mortality as these hemorrhagic complications can be difficult to predict, may occur suddenly, and also limits the therapeutic use and overall benefit of anticoagulation. Bleeding complications also increase the length of hospital stay and escalate the costs of medical care, and even minor bleeding can lead to inconveniences to the patient [1, 2].

The most distressing complication of anticoagulation therapy is major bleeding. It is defined by the International Society of Thrombosis and Haemostasis (ISTH) as fatal bleeding or symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome. It is also defined as a fall in the hemoglobin levels greater than 2 g/dL or more and/or a state that requires transfusion of two or more units of whole blood or red blood cells [3].

Clinically relevant nonmajor bleeding is defined by the ISTH as any sign or symptom of hemorrhage, e.g., more bleeding than would be expected for a clinical circumstance. It also includes bleeding found by imaging that does not fit the ISTH definition for major bleeding but does meet at least one of the following criteria: requiring medical intervention by a healthcare provider, leading to hospitalization or an increased level of care, or prompting a face-to-face evaluation [4].

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Incidence of Bleeding

It is well accepted that the first few months of anticoagulation treatment are associated with a higher rate of bleeding. The incidence of bleeding is dependent on a number of factors including older age, history of bleeding or recent bleed, cancer, uncontrolled hypertension, prior stroke, renal insufficiency, liver disease, alcohol abuse, or a platelet count less than 100,000 K/uL. In addition, the concomitant use of antiplatelet agents, poor anticoagulation control, a tendency to fall or recent surgery, and trauma increase the risk of bleeding. Insufficient patient education and information along with poor compliance are additional risk factors.

Major bleeding is the most dreaded complication of anticoagulant therapy. It has a case fatality rate (defined as the proportion of patients who die as a consequence of a particular condition) ranging from 13% to 20.2% with the highest risk of bleeding during the first 7–10 days of therapy [5–8].

Linkins et al. reported case-fatality rates of major bleeding at 13.4% [5]. In the RIETE (Registro Informatizado de Enfermedad TromboEmbolica) registry involving 41,826 consecutive patients treated for venous thromboembolism, the case fatality rate was 20.2% during the first 3 months of anticoagulation and remained relatively stable at 19.7% over a mean duration of anticoagulation of 7.8 ± 0.6 months [6]. The most common sites of 1077 major bleeding events reported in the RIETE registry were gastrointestinal (GI) (40%), central nervous system (19%), hematoma (9%), muscular (9%), genitourinary (8%), and retroperitoneal (7%).

Carrier et al. performed a systematic review of 69 articles (13 prospective cohort studies and 56 randomized control trials) involving case fatality rates of major bleeding events among patients with venous thromboembolism (VTE) and reported fatal major bleeding events at a rate of 0.2%, with a case fatality rate of 11.3% during the first 3 months of anticoagulation [9]. Gomez-Outes et al. also reported case fatality rates of bleeding in over 35,000 patients receiving direct oral anticoagulants (DOACs) versus standard therapy with a parenteral anticoagulant and vitamin K antagonist (VKA) for initial and extended treatment of venous thromboembolism. They reported major bleeding at (1.8%/yr. vs. 3.1%/yr.), fatal bleeding (0.1%/yr. vs. 0.3%/yr.), and case-fatality rates of (6% vs. 10%/yr.) all lower with DOACs than standard anticoagulation therapy [10].

Incidence of Major Bleeding During Initial Anticoagulation with Heparin, LMWH, or Fondaparinux

Anticoagulation can be divided into different phases: initial anticoagulation (days 0–10 of therapy); the first 3 months of treatment; or extended or long-term therapy (greater than 3 months). The reported incidence of major bleeding with heparin or low molecular heparin (LMWH) in combination with a loading dose of a VKA in studies of 3500 patients during the first 10 days of anticoagulation was 1.2% for LMWH and 2% unfractionated heparin [7]. In a randomized trial of fondaparinux or

enoxaparin for the initial treatment (patients received at least 5 days of one of these parenteral anticoagulants) of symptomatic deep venous thrombosis involving 2205 patients, major bleeding occurred in 1.1% of patients receiving fondaparinux and 1.2% of patients receiving enoxaparin [11]. A similar study comparing fondaparinux versus unfractionated heparin for the initial treatment of pulmonary embolism (PE) (also of at least 5 days) involving 2213 patients reported major bleeding in 1.3% of the patients treated with fondaparinux and 1.1% of those treated with heparin [12].

Incidence of Major Bleeding During the First Three Months of Treatment with a Vitamin K Antagonist

Linkins et al. in a meta-analysis of 33 prospective studies involving 10,757 patients treated for at least 3 months reported that major bleeding occurred at a rate of 7.22 per 100 patient-years and fatal bleeding at a rate of 1.31 per 100 patient-years. Intracranial bleeding occurred at a rate of 1.15 per 100 patient-years and accounted for 8.7% of all major bleeding episodes, almost half were fatal. The authors reported that as many major bleeding episodes occurred during the initial 3 months of therapy as during the entire year after this period [5]. This clustering of bleeding events at the start of anticoagulation (three of four occurred during the first 3 weeks of treatment) implied these individuals had an underlying predisposition to bleeding [5].

Incidence of Major Bleeding with the Direct Oral Anticoagulants

According to Klok et al., pooled results of five multicenter randomized controlled trials (RCT) involving 12,197 patients showed that DOACs had a superior safety profile and the risk of major bleeding over a 6 month treatment period was 1.1% with a case-fatality rate of 5.3% compared to LMWH/VKA major bleeding rate of 1.7% and case-fatality rates of 10% [7]. The authors pointed out that the risk of major bleeding randomized to LMWH/VKA treatment was lower than reported in historical studies.

In a meta-analysis of 12 RCTs involving 102,607 patients including individuals with VTE and atrial fibrillation, major bleeding was reported with the DOACs as approximately 30% lower than VKAs [13]. The investigators determined that the DOACs were associated with less major bleeding, fatal bleeding, intracranial bleeding, clinically relevant nonmajor bleeding, and total bleeding [13]. In a systematic review of 27,127 patients, Gomez-Outes et al. reported that the main benefit of the DOACs was the reduction of more severe bleeding compared to the VKAs [14]. They reported an absolute risk reduction in the order of 0.5% for major bleeding, and between 0.08% and 0.15% for fatal bleedings and intracranial bleedings respectively [14].

Considerations Prior to Initiation of Anticoagulation Therapy

It would be helpful to estimate the bleeding risk for each individual patient in clinical practice before starting anticoagulation, allowing the physician to assess the risks and benefits of therapy and adapt their management accordingly [2]. This process should not be underemphasized and must include a thorough history and complete physical examination as well as a review of their medications and basic laboratory tests.

Inquiring as to a history of easy bruising, gingival bleeding, epistaxis, hematuria, hematochezia, melena, hemarthrosis, or muscle hematomas is advised. In addition, a family history of bleeding or the patient's previous history of bleeding, spontaneous bleeding, or a previous requirement for blood transfusions during or after surgeries or interventions should be noted.

A review of the patient's medications should also be obtained. Questioning if the patient is taking an anticoagulant or any of the antiplatelet agents including aspirin, the nonsteroidal anti-inflammatory drugs (NSAIDs), the selective cyclooxygenase (Cox)-2 inhibitors (celecoxib), $P2Y_{12}$ inhibitors (ticagrelor, prasugrel, clopidogrel, and cangrelor), thrombin receptor antagonists (vorapaxar), or phosphodiesterase inhibitors (dipyridamole) should be done. The patient should be asked if they are taking any of the following herbal medications: ginkgo biloba, ginseng, saw palmetto, or garlic[15, 16]. Also whether the patient will accept blood products if bleeding develops should be verified.

A thorough physical examination should also be completed with particular attention to dermatological findings (ecchymosis, petechiae), or bleeding from the nose, gums, intravenous lines, nasogastric tubes, foley catheter or other sites.

A number of laboratory studies should be obtained including a complete blood count (CBC) with platelet count and differential, and a peripheral blood smear if the CBC is abnormal. Other tests including renal and liver functions and coagulations studies including prothrombin time (PT) or international normalized ratio (INR), and activated partial thromboplastin time (PTT) are recommended. A D-dimer, fibrinogen level and thrombin time, although not part of routine ordering, may be considered under special circumstances.

Bleeding Risk Considerations Prior to Initiation of Anticoagulant Therapy

There are a number of clinical prediction rules that may assist the clinician prior to the initiation of anticoagulant therapy to help determine which patient is more likely to develop bleeding complications. Landefeld et al. identified and preliminarily validated four predictors of major bleeding in 617 hospitalized patients starting anticoagulation therapy to prevent new thromboembolism. There were 65 patients with deep venous thrombosis (DVT) and 44 with PE [17]. The four independent risk factors for major in-hospital bleeding included comorbid conditions other than the indication for anticoagulation therapy (specific signs of heart, liver or kidney

dysfunction, cancer, and severe anemia); the use of heparin in patients 60 years or older; the intensity of anticoagulation therapy measured by the PT or PTT; and worsening of liver dysfunction during treatment [17]. The authors concluded that these specific risk factors may lead to rational risk-reduction strategies for weighing the risk versus benefits of anticoagulation therapy in each patient (17a). Byeth et al. evaluated the accuracy and clinical utility of the Outpatient Bleeding Risk Index in 264 outpatients starting warfarin and found four independent risk factors for major bleeding: age 65 years or greater; history of GI bleeding; history of stroke; and one or more of four specific comorbid conditions including a recent myocardial infarction, anemia with a hematocrit less than 30%, renal impairment with a creatinine level greater than 1.5 mg/dL, or diabetes mellitus [18]. The Outpatient Bleeding Risk Index prospectively classified patients according to the risk of major bleeding and performed better than the clinician's assessment [18]. Wells et al. also used the Outpatient Bleeding Risk Index in patients treated for DVT and PE [19]. Using the same parameters as Byeth et al., they found that the Outpatient Bleeding Risk Index discriminated between low- and moderate-risk patients and could be used to guide decisions on the optimal duration of anticoagulation [19]. Landefeld et al., in a later study, estimated the probability of major bleeding in hospitalized patients using their bleeding risk index before starting anticoagulation therapy. Their study, involving over 1000 patients established four independent risk factors including serious cardiac issues (myocardial infarction, hypotension) as well as liver and renal insufficiency, severe anemia, or cancer [1]. Patients that were 60 years of age or older had a PT or PTT ratio of 3 or greater, and worsening liver dysfunction during therapy was an additional risk factor. Major bleeding occurred in 6% of their overall patient population prior to discharge; however, the bleeding risk index predicted major bleeding in 3% of low-risk patients, 16% of 96 middle-risk patients, and 19% of 63 high-risk patients during hospitalization. The authors determined that the bleeding risk index performed as well as physicians' predictions and management could have been improved in 86% of the high-risk population group by integrating this risk assessment with the physicians' estimates. The authors also felt that bleeding might have been prevented by improving therapy: avoiding over-anticoagulation and NSAIDs, eliminating non-essential invasive procedures, and monitoring anticoagulation therapy while observing for signs of bleeding more closely [1].

Kuijer and colleagues also predicted the risk of bleeding before starting anticoagulation during treatment for VTE. They constructed and validated a bleeding risk prediction score based on three easily obtainable clinical variables [2]. These included age, sex, and the presence of malignancy. Patients were classified as low-risk, moderate-risk, or high-risk patients using these three variables, and the authors were able to identify a subgroup of patients who had a higher risk of developing hemorrhagic complications. In their model, one-fifth of the patients were categorized as high-risk for bleeding and developed bleeding rates six to seven times higher than lower risk individuals. They concluded that these variables allowed for a clinically meaningful bleeding risk categorization of patients who are started on anticoagulation therapy and suggested that aiming for a lower INR target, closer laboratory monitoring, and careful use of concomitant medications with this subgroup may decrease their risk of bleeding.

A score to predict the risk of major bleeding within the first 3 months of anticoagulation therapy was developed based on findings from the RIETE Registry and involved over 19,000 patients. Six factors were found to be independently associated with a risk for major bleeding and points were given for each of these categories. The categories included a recent major bleed, creatinine level greater than 1.2 mg/dl, anemia, cancer, a clinically overt pulmonary embolism, or age greater than 75 years [20]. Patients were classified as low-, intermediate-, or high-risk patients for major bleeding. Major bleeding occurred in 314 (2.4%) of patients and one of every three cases was fatal. The authors concluded that this information would be helpful to physicians weighing the risks and benefits of prescribing long-term anticoagulation for their patients [20].

In a more recent study from the RIETE registry consisting of nearly 25,000 patients, nine patient and laboratory characteristics were identified to help stratify the risk of fatal bleeding into low-, moderate- and high-risk categories during their first 3 months of anticoagulation [21]. These characteristics not only included five of the six factors mentioned in the earlier study listed above but also included immobility for 4 or more days, a platelet count less than 100,000 K/uL, an abnormal prothrombin time, and distal DVT. There were 546 (2.24%) major bleeds of which 135 (0.55%) were fatal. Gastrointestinal bleeding (40%) was the most common site followed by intracranial bleeding (25%). Nearly two-thirds of the major bleeds occurred in patients with a low-risk score (incidence of fatal bleeding of 0.16%), while one-third had a moderate-risk score (incidence of fatal bleeding 1.3%) and 2% had a high-risk score (incidence of fatal bleeding of 4.24%). Most major bleeding events occurred during the first 30 days of therapy and the authors concluded that using this clinical prediction rule might identify those individuals at risk for fatal bleeding and could lead the physician to consider other options such as withholding anticoagulation altogether, lowering the intensity of anticoagulation and/or monitoring the patient more closely for signs and symptoms of bleeding [21].

Klok et al. reviewed five different bleeding-prediction scores to externally validate and compared their predictive powers in 448 consecutive patients with acute PE [8]. Two of the studies involved patients with VTE and three involved patients with atrial fibrillation [8]. Twenty patients (4.5%) suffered major bleeding over a 30-day period and the authors found that the highest risk of bleeding was within the first 7 days of treatment. The scores were made up from the following scores: Kuijer, RIETE, HEMORR$_2$HAGES, HAS-BLED, and ATRIA**.** Unfortunately, the predictive power of the scores was poor and the authors concluded that the current scoring systems have insufficient accuracy to predict overall anticoagulation-associated bleeding and that using them was no better than flipping a coin [8].

A recent study using six variables to predict major bleeding in patients referred to as VTE-BLEED was derived after analysis of consecutive patients in the two RE-COVER trials from patients who were randomized to treatment with dabigatran or warfarin. It was the first risk assessment model for predicting long-term (between day 30 to day 180) anticoagulant-associated major bleeding in VTE patients that has been validated in two different clinical trials and for three different drug classes including the direct thrombin inhibitors, factor Xa inhibitors, and vitamin K antagonists [22]. This was a post-hoc study of 8240 study patients from the randomized,

Table 1 Risk factors influencing bleeding risk

Male sex
Maximal PT or PTT times 2 or more times control
Recent bleeding event
Pulmonary embolism
Immobility
History of stroke
Female sex
Liver dysfunction worsening during therapy
Creatinine 1.1 mg/dL
Distal DVT
Peptic ulcer disease
Anemia
Platelets <100,000 dL
Alcohol abuse
Malignancy
Hypertension
Heparin use in patients ≥60 years of age
Age >60 years or >75 years

double-blind, double-dummy, Hokusai VTE study comparing edoxaban versus warfarin. The variables included actiVe cancer, males with uncontrolled hyperTension at baseline, anaEmia, and history of BLeeding, agE ≥ 60 years and rEnal Dysfunction and as in other studies, patients received points dependent on the category of low bleeding or high bleeding risk [22]. Patients considered to be at a low risk for bleeding had a bleeding score of <2 points while those at a high risk of bleeding had a bleeding score ≥2. Those identified to be of high risk had a fourfold increased risk of bleeding, and the authors concluded that this scoring risk assessment tool could be used to increase awareness of the patient's bleeding risk. If the score indicates high risk, increased vigilance should be observed [22].

Assembling the different risk factors listed above from the referenced clinical prediction rules for bleeding, there are 19 distinct factors that may place patients at increased risk for bleeding (Table 1).

What Do the Guidelines Tell Us with Regard to Bleeding Risk? How Does the Physician Decide Which Risk Factors to Consider?

The European Society of Cardiology (ESC) makes no recommendation regarding the use of a specific standardized bleeding risk assessment tool for overseeing anticoagulation therapy [23]. The American College of Chest Physicians (ACCP) refers to no less than 18 risk factors for bleeding and places them into low-, moderate- and high-risk categories [24]. Patients at low risk for bleeding have none of the factors listed below, while patients at moderate risk have one risk factor. If two or more risk factors are present, the patient has a high bleeding risk. Compared with low-risk patients, moderate-risk patients are assumed to have a twofold risk and high-risk patients are assumed to have an eightfold risk of major bleeding. Recommendations suggest that the physician weigh in the risks versus benefits for anticoagulation in the high-risk population. It is important to note, however, that this categorization of risk of bleeding has never been externally validated (Table 2).

Table 2 Risk factors for bleeding with anticoagulant therapy and estimated risk of major bleeding in low-, moderate-, and high-risk categories

Age >65 years			
Age >75 years			
Previous bleeding			
Cancer			
Metastatic cancer			
Renal failure			
Liver failure			
Thrombocytopenia			
Previous stroke			
Diabetes			
Anemia			
Antiplatelet therapy			
Poor anticoagulation control			
Comorbidity and reduced functional capacity			
Recent surgery			
Frequent falls			
Alcohol abuse			
Nonsteroidal anti-inflammatory drugy			
Estimated absolute risk of major bleeding			
	Low risk (0 risk factors)	Moderate risk (1 risk factor)	High risk (≥2 risk factors)
Anticoagulation (0–3 months)			
Baseline risk (%)			
Increased risk (%)	0.6	1.2	4.8
Total risk (%)	1.0	2.0	8.0
Anticoagulation after first 3 months	1.6	3.2	12.8
Baseline risk (%/y)			
Increased risk (%/y)	0.3	0.6	≥2.5
Total risk (%/y)	0.5	1.0	≥4.0

Incidence of Major Bleeding Associated with Thrombolytic Therapy

Determining the risk of bleeding for patients receiving thrombolytic therapy is complicated by several factors. In a review by Daly et al. comprising 35 different studies, major bleeding varied between 0% and 32.9%, while intracranial hemorrhage ranged from 0% to 7.4% [25]. Data from this review was made up of different thrombolytic agents (urokinase, streptokinase, alteplase, reteplase, and tenecteplase), different dosing regimens, the definition of major bleeding varied among studies, sample sizes ranged from 7 to 525 patients, and bleeding results reported included vascular access sites, generally no longer considered a major risk factor for bleeding [25].

A recent meta-analysis comprising 2115 individuals reported major bleeding at 9.24% receving thrombolytic therapy versus 3.42% with standard anticoagulation therapy, while intracranial hemorrhage was reported at 1.46% compared to 0.19% with anticoagulation therapy [26]. A Cochrane database systemic review reported major bleeding rates at 10.4% with an intracranial hemorrhage rate of 0.5%, while another small review of 62 patients showed 45% major bleeding events and 2% intracranial hemorrhage rates [27, 28]. In the latter trial, patients with one or more risk factors for bleeding had a five times higher risk for bleeding. These individuals with major bleeding also predictably had a higher mortality rate while in the intensive care unit, as well as showed higher overall mortality, increased length of hospital stay, and higher costs [28].

Patients with major bleeding frequently had recent major surgery, an elevated INR greater than 1.7 at initiation of therapy, or one or more of the following factors for bleeding: older age, African-American, lower body weight, female sex, or poorly controlled hypertension [28, 29].

A more recent trial on fibrinolysis for patients with intermediated-risk PE (PEITHO) involving 1005 patients reported major extracranial bleeding compared to placebo at 6.3% versus 1.2%, major bleeding at 11.5% versus 2.4%, and hemorrhagic stroke at 2.0% versus 0.2% [30].

There are a number of absolute and relative contraindications for thrombolytic therapy for the treatment of VTE (Table 3) [24].

Table 3 Absolute and relative contraindications for the use of thrombolytics

Absolute contraindications
Structural intracranial disease
Previous intracranial hemorrhage
Ischemic stroke within 3 months
Active bleeding
Recent brain or spinal surgery
Recent head trauma with fracture or brain injury
Bleeding diathesis
Relative contraindications
Systolic blood pressure >180 mmHg
Recent bleeding (non-intracranial)
Recent invasive procedure
Anticoagulated (VKA therapy)
Pericarditis or pericardial fluid
Pregnancy
Low body weight (e.g., <60 kg)
Black race
Diastolic blood pressure >110 mmHg
Recent surgery
Ischemic stroke more than 3 months ago
Traumatic cardiopulmonary resuscitation
Diabetic retinopathy
Age >75 years
Female

Summary

Physicians should obtain a thorough history and perform a detailed physical exam prior to the initiation of anticoagulation or thrombolytic therapy. They should obtain routine laboratory studies including a complete blood count, renal and liver function studies, and coagulation tests including a PT/INR, aPTT, and fibrinogen levels if thrombolytic agents are to be employed.

While the patient is receiving therapy, one should discourage the use of concomitant anticoagulants or NSAIDs or platelet inhibitors. Close attention to blood pressure should be maintained at all times and the clinician should weigh the risk factors for bleeding against the benefit of anticoagulation or thrombolytic therapy for each and every patient prior to starting therapy. In addition, patients should be carefully educated regarding their therapeutic options as well as the risks and benefits of those treatments.

There are a number of strategies one should implement to minimize bleeding risks with anticoagulation or thrombolytic therapy. Withholding anticoagulation altogether and placement of an inferior vena cava filter may be an option. Administering anticoagulants at a lower intensity may also be a consideration. Avoiding non-essential procedures, monitoring therapy meticulously, and observing diligently for signs of bleeding, as well as avoiding over-anticoagulation with heparin, low molecular weight heparin, fondaparinux, warfarin, or the DOAC, are crucial.

In patients considered for thrombolytic therapy, the clinician should screen actively for absolute contraindications while performing an individualized assessment of the benefits and risks of this therapy for each patient. In addition, administration techniques (avoid bolusing) and use of different reperfusion strategies such as catheter-based interventions or lower-dosage may be helpful. Ultimately, the decision to proceed with therapy lies in the hand of the provider based on each individual's risk factor [28].

Bleeding is the most important complication of anticoagulation therapy. Although no reliable tool is available to assess all bleeding risks during therapy, known risk factors for increased risk of bleeding should be taken into account on an individual basis when starting anticoagulation and while the patient is on anticoagulation [31].

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Treatment for Pulmonary Embolism: Anticoagulation Selection and Duration

Megan E. Barra, Russel J. Roberts, and Rachel P. Rosovsky

Introduction

Venous thromboembolism (VTE), which constitutes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity and mortality worldwide. There are approximately 900,000 cases of VTE and up to 100,00 deaths from PE in the United States each year [1, 2]. Anticoagulation is the mainstay of therapy for VTE, and up until a decade ago, treatment options were limited to parenteral agents including unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), fondaparinux, and vitamin K antagonists (VKAs). The emergence of direct oral anticoagulants (DOACs) offers patients a more convenient and accessible alternative. The rapid onset of action, short half-life, predictable pharmacokinetics (PK) and pharmacodynamics (PD), fixed dosing, few drug and food interactions, decreased bleeding risk, and comparable efficacy to warfarin/heparin lend agency to the use of DOACs for the treatment of VTE [3–7]. Currently, the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban and the direct thrombin inhibitor (DTI), dabigatran, are approved and used routinely for the prevention and treatment of VTE. The purpose of this chapter is to provide essential information and guidance on the practical management of anticoagulant options for the treatment and secondary prevention of PE. It highlights the factors involved in deciding on the most appropriate anticoagulant as well as different doses and regimens, use in special populations, and recommended duration of treatment.

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Historical Perspective

The first documented description and treatment of a DVT dates back to the Middle Ages, with a 20-year-old male who developed pain and swelling in his calf which progressed to leg ulcers [8, 9]. The young patient was advised to visit the tomb of Saint Louis in the church of Saint Denis, and while there, he rubbed dust onto the ulcers which healed them. Subsequent therapies focused on what was believed to be the mechanism behind thrombus formation [10, 11]. The idea that DVT was caused by the retention of evil humors was held until the end of the nineteenth century and led to the technique of bloodletting, often with leeches [12]. Its popularity continued when inflammation of the vein was considered a likely cause of DVT. During this time, venous ligation was also practiced to thwart clot propagation [13]. Eventually, in 1856, Rudolph Virchow described the consequences of a PE that migrated from the venous circulation, and this later formed what it known as Virchow's triad [14]. This triad of venous stasis, endothelial injury, and hypercoagulability has become widely accepted as a model for understanding the pathophysiology of thrombosis. With this appreciation, several new therapies were discovered. Heparin was the first commercially available parenteral anticoagulant [15, 16]. Shortly after, dicoumarol was discovered as the active ingredient in spoiled sweet clover which caused spontaneous fatal bleeding in cattle [16, 17]. In 1954, a coumarin variant initially used as a rodenticide, warfarin, was developed and adopted to allow for extended treatment for DVT. Subsequently, LMWH was discovered in 1976 and changed the management of DVT/PE by reducing the need for hospitalization because it was given subcutaneously, rapidly achieved anticoagulation effect, did not require therapeutic drug monitoring, and could be used as monotherapy or short term to bridge to warfarin [18]. LMWH has also been effective and widely used in preventing thromboembolic events in surgical, medically ill hospitalized, cancer patients. In 2001, the synthetic pentasaccharide, fondaparinux sodium, was approved to treat DVT and PE. A decade later, the DOACs followed. Notably, prior to the availability of DOACs, warfarin was the most widely used anticoagulant in the world.

Overview of Anticoagulants

Parenteral and oral anticoagulant therapies have emerged as the mainstay of therapeutic treatment options for the management of PE. Parenteral anticoagulation options include intravenous (IV) UFH, subcutaneous LMWHs (e.g., enoxaparin and dalteparin), and subcutaneous fondaparinux. Oral anticoagulation options include DOACs (e.g., apixaban, dabigatran, edoxaban, and rivaroxaban) and VKA (e.g., warfarin). An overview of pharmacokinetic (PK) and pharmacodynamic (PD) properties is presented in Tables 1 and 2 and Fig. 1.

Table 1 Parenteral anticoagulant therapy pharmacologic properties [21, 22, 74, 77, 80, 114–116]

	UFH	Enoxaparin	Fondaparinux	Argatroban	Bivalirudin
Primary mechanism of action	AT-III mediated inhibition of factor IIa and Xa (1:1 ratio)	AT-III mediated inhibition of factor Xa and to lesser extent factor IIa (3:1 ratio)	Antithrombin III mediated inhibition of factor Xa	Factor IIa inhibitor	Factor IIa inhibitor
Standard dose for initial PE treatment	80 unit/kg IV bolus followed by 18 units/kg/hr infusion, titrated to institutional PTT goal	1 mg/kg SQ twice daily or 1.5 mg/kg SQ once daily	<50 kg: 5 mg SQ once daily 50–100 kg: 7.5 mg once daily >100 kg: 10 mg once daily	0.25–2 mcg/kg/min	0.15 mg/kg/hr
Dose adjustments	No dose adjustments necessary	CrCl <30 mL/min: decrease dose to 1 mg/kg SQ once daily	Avoid use if CrCl <30 mL/min	Dose adjustment needed in hepatic dysfunction	Dose adjustment needed in renal dysfunction
Volume of distribution	40–70 mL/kg	4.3 L	7–11 L	174 mL/kg	0.24 L/kg
Metabolism	Thought to occur in liver and spleen via depolymerization and desulfation in reticuloendothelial system	Hepatic via desulfation and/or depolymerization	Primarily excreted as unchanged drug in the urine	Hepatic via hydroxylation and aromatization	Proteolytic cleavage (80%)
Elimination	Rapidly via nonrenal mechanisms	10% (active) 40% (nonactive)	77% unchanged in urine	Urine (22%; 16% unchanged)	Urine (20% unchanged)
Administration considerations	Contraindicated if recent history of HIT	Contraindicated if recent history of HIT		May falsely elevate the INR	May falsely elevate the INR
Half-life	1.5 hr (range 1–2 hr)	4.5–7 hr	17–21 hr, prolonged in renal impairment	Normal hepatic function: 39–51 min Hepatic impairment: 181 min	GFR >60 mL/min: 25 min GFR 30–59 mL/min: 34 min GFR <30 mL/min: 57 min Dialysis: 3.5 hr
Reversal agent	Protamine	Protamine	No specific reversal agent available	No reversal agent available	No reversal agent available

AT-III antithrombin-III, *hr* hour, *GFR* glomerular filtration rate, *HIT* heparin induced thrombocytopenia, *INR* international normalized ratio, *kg* kilogram, *L* liter, *mcg* microgram, *mg* milligram, *min* minute, *mL* milliliter, *PE* pulmonary embolism, *PTT* partial thromboplastin time, *SQ* subcutaneous

Table 2 Oral anticoagulant therapy pharmacologic properties [29–32, 103, 117]

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Mechanism of action	Factor Xa inhibitor	Factor IIa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Vitamin K antagonist (inhibits factors II, VII, IX, and X and endogenous anticoagulant proteins C and S)
Initial treatment dosing	10 mg ever twice daily for 7 days followed by 5 mg twice daily	After ≥5 days of initial parenteral therapy 150 mg twice daily	After ≥5 days of initial parenteral therapy 60 mg once daily	15 mg twice daily for 21 days followed by 20 mg once daily with food	Once daily administration with dose individualized based on INR results
Dose adjustments	[a]Reduce apixaban dose by 50% if concurrent strong dual CYP3A4 and P-gp inhibitors and initial dose >2.5 mg twice daily	None	[b]30 mg once daily if weight ≤60 kg, CrCl 15–50 mL/min, or concomitant specific P-gp inhibitors	None	None
Standard dose for extended treatment	2.5 mg twice daily after at least 6 months of therapeutic anticoagulation	Not studied	10 mg once daily after at least 6 months of therapeutic anticoagulation	No dose adjustment	No dose adjustment
Hepatic impairment	Use with caution in Child–Pugh class B Avoid if Child–Pugh class C	Use with caution in Child–Pugh class B Avoid if Child–Pugh class C	Avoid if Child–Pugh class B or C	Avoid if Child–Pugh class B or C	–
Renal impairment	Use with caution in CrCl ≤15 mL/min	Avoid if CrCl ≤30 mL/min	[c]Avoid if CrCl ≤15 mL/min	Limited data with use in CrCl 15–30 mL/min, consider alternatives Avoid use in CrCl <15 mL/min	–

Table 2 (continued)

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Special considerations	–	Avoid if dyspepsia	–	[d]Must be administered with food	Significant drug–drug and drug–food interactions
Time to peak effect	3–4 hr	1.5 hr	1–2 hr	2–4 hr	72–96 hr
Half-life	12 hr	12–17 hr	10–14 hr	5–9 hr	R-warfarin: 37–89 hr S-warfarin: 21–43 hr
Oral bioavailability	50%	3–7%	62%	[c]Dose-dependent; 20 mg tablet 66% (without food)	100%
Protein binding	87%	35%	55%	92–95%	99%
Volume of distribution	21 L	50–70 L	107 L	50 L	10 L
Metabolism	Major: CYP3A4 Minor: CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2J2 (25% unchanged)	Esterase-catalyzed hydrolysis	Minimal metabolism by hydrolysis, conjugation, and oxidation by CYP3A4	Major: CYP3A4/5 and CYP2J2 and hydrolysis	CYP2C9, CYP2C19, CY2C8, CYP2C18, CYP1A2, CYP3A4
Clearance	25% renal	80% renal	50% renal	36% renal	Minimal renal elimination
Dialyzable	Small	Yes	No	No	No
P-gp substrate	Yes	Yes	Yes	Yes	No
Administration considerations	Without regard to meals	Without regard to meals	Without regard to meals	Take with food	Without regard to meals
Pro-drug	No	Yes	No	Yes	No
Absorption site	Proximal small intestine, some gastric	Lower stomach and duodenum	Proximal small intestine	Lower stomach and proximal small intestine, some gastric absorption	Proximal small intestine

(continued)

Table 2 (continued)

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	Warfarin
Laboratory measurements	Anti-Xa	Dilute thrombin time	Anti-Xa	Anti-Xa	INR
Reversal agent	Andexanet alfa (specific) or 4F-PCC (nonspecific)	Idarucizumab (specific)	4F-PCC (nonspecific)	Andexanet alfa (specific) or 4F-PCC (nonspecific)	Phytonadione (vitamin K) ± 4F-PCC or FFP (specific)

4F-PCC four factor prothrombin complex concentrate, *CrCl* creatinine clearance, *hr* hours, *INR* international normalized ratio, *FFP* fresh-frozen plasma, *L* liter, *min* minute, *mL* milliliter, *mg* millilgram, *P-gp* p-glycoprotein

Notes

[a]Strong dual CYP3A4 and P-glycoprotein inhibitors (e.g., ketoconazole, itraconazole, and ritonavir)

[b]Administer edoxaban 30 mg once daily if concomitant P-glycoprotein inhibitors verapamil, quinidine, azithromycin, clarithromycin, erythromycin, oral itraconazole, or oral ketoconazole. Dose may be increased to 60 mg once daily once offending drug interaction agents are discontinued if no other clinical criteria (body weight ≤60 kg or CrCl 15–50 mL/min) are met

[c]In patients with atrial fibrillation, edoxaban should not be used if CrCl >95 mL/min due to increased risk of ischemic events. There are no data available to suggest increased risk of recurrent VTE in patients with PE and CrCl >95 ml/min, cautious use is advised

[d]AUC of rivaroxaban is increased by 39% and Cmax 76% when taken with food

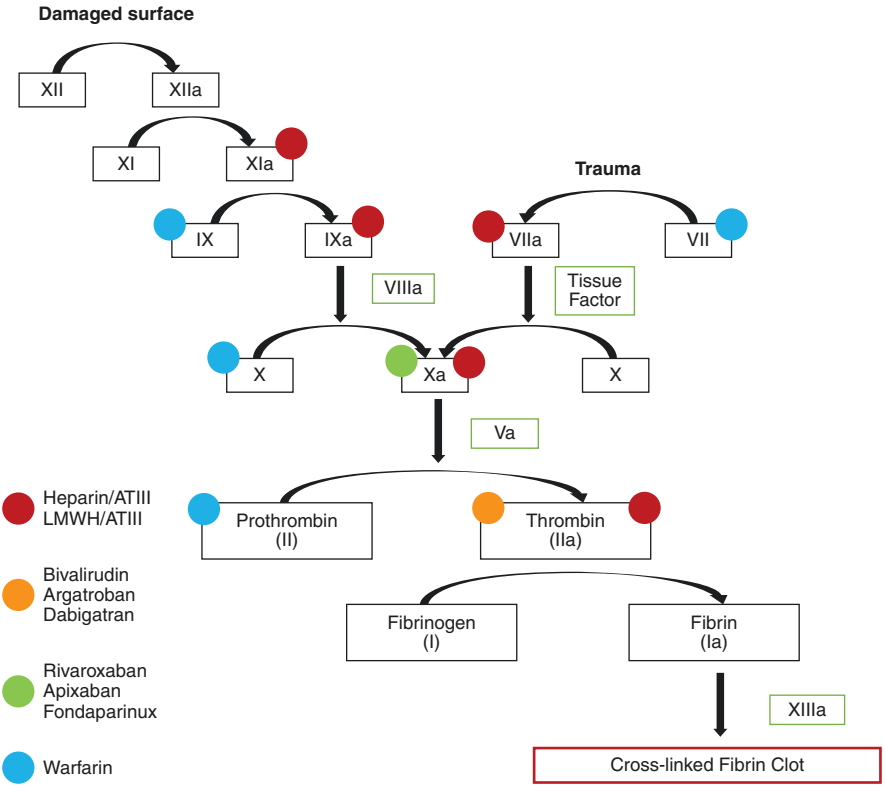

Fig. 1 Anticoagulation agents mechanism of action

Parenteral Agents

Heparinoids and Fondaparinux

Parenteral agents have traditionally been the initial treatment modality for hospitalized patients with VTE. UFH's main advantage is its short half-life and easy reversibility. It is titrated to therapeutic levels according to institutional partial thromboplastin time (PTT) guidelines or anti-Xa values [19]. Limitations of UFH include its interindividual variability in dose response and the potential complication of heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis (HITT) [20]. As a smaller molecule, LMWH causes fewer immunologic thrombocytopenia, does not bind to plasma proteins, and thus has more reliable PK properties [20]. These properties make it an attractive alternative to UFH. Laboratory monitoring for LMWH is typically not required, unless concern for under- or overexposure in select patients. Since its approval in 1990s, LMWH has allowed patients with low-risk VTE to be treated in the outpatient setting. An additional parenteral agent, fondaparinux, is a synthetic inhibitor of factor Xa [21]. The advantage of fondaparinux is its once daily and fixed (weight-based) dose (Fig. 2).

Direct Thrombin Inhibitors (DTIs)

Two commercially parenteral DTIs are available in the United States, argatroban and bivalirudin. Unlike UFH, argatroban and bivalirudin are not inactivated by platelet factor 4 (PF4) [22, 23]. The IV DTIs have been typically reserved for treatment in patients with HIT or HITT [24]. Argatroban is approved by U.S. Food and Drug Administration (FDA) for general HIT and for percutaneous coronary

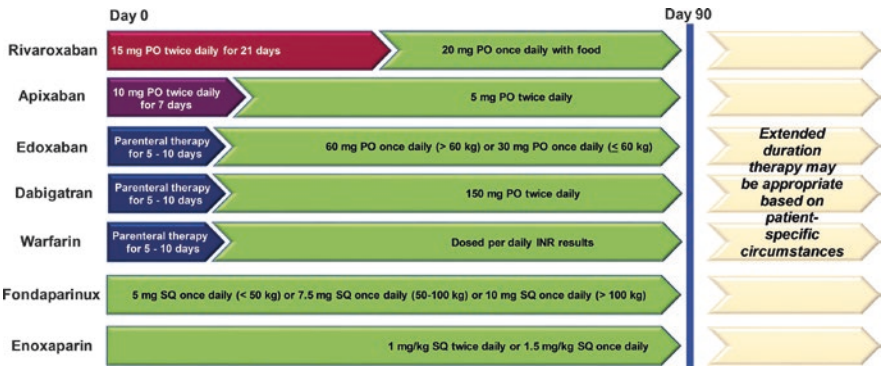

Fig. 2 Treatment strategies for pulmonary embolism (acute and extended). *Abbreviations*: PO, per os (by mouth); SQ, subcutaneous; kg, kilograms; mg, milligrams; INR, international normalized ratio. *Note*: Data represent usual dose in patients with normal body weight and renal function. Dose adjustments may be required for select patient conditions, see Tables 1 and 2 for more information. Parenteral therapy may include intravenous unfractionated heparin, subcutaneous low-molecular-weight heparin (e.g., enoxaparin), or fondaparinux

intervention (PCI) in patients who have or are at risk of developing HIT. Conversely, bivalirudin is only FDA approved for PCI in patients with or without HIT/HITT but is commonly used off-label in patients with general HIT [24]. IV DTIs may also be an alternative to UFH or LMWH in patients with antithrombin III deficiency displaying signs of heparin resistance [25]. For the treatment of VTE, both IV DTIs are administered as continuous infusions and titrated according to PTT values with therapeutic goals determined by institutionally calibrated PTT assays [24].

Oral Anticoagulants

Vitamin K Antagonists

Parenteral UFH or LMWH followed by oral VKA has historically been considered conventional treatment for PE [26]. VKA exhibits large interindividual variability in dose–response and coupled with the narrow therapeutic index requires regular therapeutic drug monitoring making treatment challenging [27]. Furthermore, due to the delayed onset of antithrombotic effect, overlap with parenteral therapies for approximately 4–5 days is necessary as a therapeutic international normalized ratio (INR) may not confer protection early in the treatment course [28].

Direct-Acting Oral Anticoagulants (Apixaban, Edoxaban, Rivaroxaban, and Dabigatran)

Since the first approval in 2010, DOACs have been increasingly used for the treatment and secondary prevention of VTE due to their ease of use and enhanced safety profile compared to VKA. Apixaban, dabigatran, edoxaban, and rivaroxaban do not require routine monitoring for and have less drug and food interactions than VKA, making them an attractive option for many patients. Apixaban, edoxaban, and rivaroxaban inhibit both free- and clot-bound factor Xa [29], while dabigatran etexilate inhibits both free- and clot-bound thrombin [27]. Oral bioavailability of dabigatran increases by 75% when capsules are opened; therefore, dabigatran should not be used in patients who are unable to swallow capsules whole [30]. Both dabigatran and edoxaban require at least 5 days of parenteral therapeutic anticoagulation therapy prior to their initiation for the management of PE (Fig. 2) [30, 31]. In contrast, apixaban and rivaroxaban may be initiated in the treatment of acute PE using an oral loading dose for a period of 7 days (apixaban) or 21 days (rivaroxaban) without an initial 5-day parenteral therapy (Fig. 2) [29, 32]. Agent-specific PK/PD parameters are further described in Table 2.

Anticoagulation agent selection should be individualized based on patient-specific factors to enhance safety and efficacy in treating acute PE. There are currently no head-to-head trials which suggest that one DOAC is more efficacious or safer than another. Thus, comorbid conditions including renal and hepatic dysfunction, extremes of body weight, bleeding risks, medication adherence behaviors, presence of drug–drug interactions, potential for invasive procedures, patient

preference, and importantly, out-of-pocket costs associated with therapy may determine optimal anticoagulant selection [33].

Treatment Paradigms

Anticoagulation therapy is the single most important therapeutic strategy in the treatment of PE. When initiated early after PE diagnosis, it is associated with up to 70% decreased risk of mortality and recurrent PE [34]. Current guidelines provide Grade 2B recommendations for DOAC therapy over VKA for long-term therapy and Grade 2C recommendation preferring VKA therapy over LMWH in patients without cancer on the basis of improved patient convenience [35]. Furthermore, reaching a therapeutic activated partial thromboplastin time (aPTT) within 24 hours of UFH initiation may also be an independent predictor of decreased mortality [34]. Despite the critical need to achieve this goal, the majority of patients with acute PE treated with guideline-recommended dosing of UFH spend most of their first 48 hours outside of the therapeutic range [36]. Proposed mechanisms of the benefit of rapid attainment of therapeutic anticoagulation include reduced rates of clot propagation and associated hemodynamic compromise or secondary thromboembolic events. Quickly achieving therapeutic anticoagulation while balancing hemorrhagic risk is vital to the success in managing PE patients. Intravenous UFH has been the mainstay of anticoagulation since it was first used in the 1930s [9]. Alternative therapeutic agents have been developed to address the limitations of heparin therapy. The following section reviews the seminal trials which led to their use in the treatment of PE.

LMWH Trials

In a randomized trial of 200 patients with PE, once daily LMWH (tinzaparin) was associated with fewer episodes of recurrent VTE and no difference in major bleeding compared to heparin [37]. Furthermore, there was no difference in recurrent VTE or major hemorrhage in a subsequent randomized controlled trial of 900 patients with symptomatic DVT, including 287 patients with PE treated, with once or twice daily LMWH versus IV UFH [38]. In patients with submassive symptomatic PE or asymptomatic PE with symptomatic DVT, LMWH was found to be noninferior to IV UFH in recurrent symptomatic VTE at completion of treatment and at 3 months [39]. Moreover, no significant differences in major bleeding complications were observed. A recent Cochrane analysis of 29 studies involving 10,390 patients found moderate-quality evidence that fixed-dose LMWH compared to UFH reduced the incidence of recurrent thrombotic complications and major hemorrhage during initial treatment of VTE [40]. Another advantage of LMWH over UFH is a lower incidence of HIT [41–43]. The ease of dosing, lack of required monitoring, rapid attainment to therapeutic levels, and less HIT make LMWH an attractive alternative to UFH.

Fondaparinux Trials

Subcutaneous fondaparinux was found to be another safe and effective alternative to IV UFH for initial treatment of PE in the MATISSE randomized controlled trial of 2213 patients diagnosed with PE [44]. Approximately 3.8% of patients in the fondaparinux group compared to 5% patients in the IV UFH group had recurrent VTE during the study period with no difference in major bleeding.

DTI Trials

Argatroban

Argatroban's FDA approval in 2000 for use in HIT was based on two multicenter, nonrandomized, open-label, historical control studies [45, 46]. Among both studies, over 700 argatroban-treated patients diagnosed with HIT or HITT were compared to historic controls with a primary composite outcome of all-cause mortality, all-cause amputation, and new thrombosis at 37 days [45, 46]. Both studies showed a reduction in the primary composite outcome for argatroban-treated patients diagnosed with HIT but did not show a significant reduction in patients diagnosed with HITT [45, 46]. Moreover, argatroban-treated patients had a more rapid platelet recovery versus controls with similar bleeding rates between groups [45, 46].

Bivalirudin

While bivalirudin is FDA approved in patients undergoing PCI with HIT [24, 47], its use in generalized HIT is only supported by retrospective analyses describing institutional use [48–50]. One study suggested that the rate of HIT-related amputation may be reduced but an increased risk of major bleeding may occur in critically ill patients [50]. Another study reported that bivalirudin dosing requirements correlate with renal function [49]. Despite data limitations, available evidence suggests that bivalirudin may be an effective and safe alternative treatment option for VTE in patients with suspected or confirmed HIT [48–50].

DOAC Trials

Several landmark trials have paved the way for mainstream introduction of DOACs for the treatment of VTE, of which PE represented 30–100% of patients enrolled (Table 3) [4, 6, 7, 51]. Additionally, extensive PE was present on initial diagnosis in approximately 25% of patients who received rivaroxaban, 38% apixaban, and 45% edoxaban. Both the oral factor-Xa inhibitors and oral DTIs were found to be

Table 3 Direct-acting oral anticoagulants landmark trials

	RE-COVER		RE-COVER II		EINSTEIN-PE		Hokusai-VTE		AMPLIFY	
	Dabigatran	Warfarin	Dabigatran	Warfarin	Rivaroxaban	LMWH+VKA	Edoxaban	Warfarin	Apixaban	LMWH+VKA
Total number patients with VTE	1273	1266	1280	1288	2419	2413	4118	4122	2691	2704
Number of patients PE PE only PE + DVT	270 (21.2) 121 (9.5)	271 (21.4) 124 (9.8)	298 (23.3) 104 (8.1)	297 (23.1) 117 (9.1)	1813 (74.9) 606 (25.1)	1823 (75.5) 590 (24.5)	1240 (30.1) 410 (10.0)	1265 (30.7) 404 (9.8)	678 (25.2) 252 (9.4)	681 (25.2) 225 (8.3)
Anatomical extent of PE Limited Intermediate Extensive Not assessable	Not reported	Not reported	Not reported	Not reported	309 (12.8) 1392 (57.5) 597 (24.7) 121 (5.0	299 (12.4) 1424 (59.0) 576 (23.9) 114 (4.7)	128 (7.8) 679 (41.2) 743 (45.0) 100 (6.1)	123 (7.4 682 (40.9) 778 (46.6) 86 (5.2)	79 (8.5) 392 (42.2) 357 (38.4) 102 (11.0)	89 (9.8) 395 (43.6) 326 (36.0) 96 (10.6)
Recurrent VTE or death	30 (2.4)	27.1 (2.5)	30 (2.3)	28 (2.2)	50 (2.1)	44 (1.8)	130 (3.2)	146 (3.4)	59 (2.3)	71 (2.7)
	HR 1.10 (0.65–1.84)		HR 1.08 (0.64–1.80)		HR 1.12 (0.75–1.68)		HR 0.89 (0.70–1.13)		RR 0.84 (0.60–1.18)	
Major bleed	20 (1.6)	24 (1.9)	15 (1.2)	22 (1.7)	26 (1.1)	52 (2.2)	56 (1.4)	66 (1.6)	15 (0.6)	49 (1.8)
	HR 0.82 (0.45–1.48)		HR 0.69 (0.36–1.32)		HR 0.49 (0.31–0.79)		HR 0.84 (0.59–1.21)		RR 0.31 (0.17–0.55)	
Major or clinically relevant nonmajor bleeding event	71 (5.6)	111 (8.8)	64 (5.0)	102 (7.9)	249 (10.3)	274 (11.4)	349 (8.5)	423 (10.3)	115 (4.3)	261 (9.7)
	HR 0.63 (0.47–0.84)		0.62 (0.45–0.84)		HR 0.90 (0.76–1.07)		HR 0.81 (0.71–0.94)		RR 0.44 (0.36–0.55)	

PE pulmonary embolism, *VTE* venous thromboembolism, *DVT* deep vein thrombosis, *LMWH* low-molecular-weight heparin, *VKA* vitamin K antagonists, *HR* hazard ratio, *RR* relative risk

Note: Data presented as no. (%) unless otherwise noted

noninferior to VKA-based anticoagulation therapy for the management of PE. Importantly, no randomized controlled trials have directly compared DOAC therapies to one another.

In the AMPLIFY trial, apixaban was associated with a significant decrease in both major and clinically relevant nonmajor bleeding (CRNMB) compared to VKA-based therapy [51]. Moreover, a subgroup analysis of the AMPLIFY trial found a reduction in all-cause hospitalizations within the first 30 days after index event in patients treated with apixaban (2.28%) versus standard therapy (3.35%), respectively (HR 0.676; 95% CI 0.488–0.935), and shorter hospital length of stay [52]. Edoxaban therapy evaluated in the Hokusai-VTE trial was also found to be superior to VKA-based therapy on the compositive safety outcome of major and CRNMB [4]. Edoxaban was associated with decreased rates of recurrent VTE in a subgroup analysis of PE patients with right ventricular dysfunction defined as a NT-proBNP >500 pg/mL (3.3% versus 6.2%, respectively; HR 0.53; 95% CI [0.28–0.98]) [4]. These data were further supported in a post hoc subgroup analysis, suggesting edoxaban may be more effective than warfarin for the prevention of recurrent VTE in patients with PE and right ventricular dysfunction [53]. A fixed dose of rivaroxaban was found to be noninferior to standard therapy with UFH or LMWH followed by warfarin in EINSTEIN-PE trial for the primary outcome of recurrent VTE. Rivaroxaban therapy was associated with a significant reduction in major but not CRNMB [6]. While dabigatran was noninferior to warfarin in both primary efficacy and safety outcomes in the RECOVER I trial, pooled analysis with the subsequent RECOVER II trial noted a significant decrease in the risk of any bleeding during treatment with dabigatran versus warfarin (HR 0.70; 95% CI [0.61–0.79]) [7, 54].

Extended Therapy

Duration of anticoagulation is one of the most frequent and important questions to address when treating patients with VTE. This decision should be individualized for each patient and should include the initial and periodic assessment of the presence of transient or persistent risk factors for recurrent VTE, as well as age, sex, obesity, and organ function (hepatic and renal). These factors should be balanced by present risk factors for bleeding during anticoagulation. This risk/benefit assessment should also include patient preferences, including cost of the anticoagulant.

In patients who had a transient risk factor that has resolved, short-term therapy (e.g., 3 months) may be reasonable. Alternatively, in patients who with an unprovoked VTE (PE or proximal DVT) or a provoked VTE with ongoing risk factors, long-term anticoagulation may be warranted. All DOACs, except for edoxaban, have been evaluated in randomized controlled trials for extended secondary VTE prevention beyond the initial 3 months. Studies investigating the use of apixaban, rivaroxaban, or dabigatran for secondary prevention of VTE demonstrated superiority in preventing the primary efficacy endpoint of symptomatic recurrent VTE as compared to placebo (AMPLIFY-EXTENSION [apixaban], EINSTEIN-EXTENSION [rivaroxaban],

RE-SONATE [dabigatran]) or aspirin (EINSTEIN CHOICE [rivaroxaban]) without a significant increase in major bleeding [3, 5, 7]. Dabigatran was also found to be non-inferior to warfarin in preventing recurrent VTE in an extended VTE prevention trial (RE-MEDY) with significantly lower rates of bleeding [26]. In a recent meta-analysis of 16 studies including 12,458 patients, extended anticoagulation with DOACs was associated with a significant reduction in overall mortality compared with observation alone [55]. Furthermore, there have been several analyses demonstrating that extended treatment with anticoagulation and, in particular, DOACs is cost-effective for the prevention of recurrent VTE in patients [56–58]. Thus, all these results support the use of extended duration of anticoagulation in select patients to reduce the lifetime risk of recurrent thrombosis and VTE-associated death.

Importantly, the duration of anticoagulation should be assessed at least annually, considering the risk for overall VTE recurrence in certain populations is high. A recent systematic review and meta-analysis of 18 studies involving 7515 patients with a first unprovoked VTE who completed at least 3 months of anticoagulant treatment found that the risk of recurrent VTE was 10% in the first year after treatment, 16% at 2 years, 25% at 5 years, and 36% at 10 years, with 4% of recurrent VTE events resulting in death [59]. Appreciating these high rates of recurrence should help guide decision-making about long-term management and enhance confidence when counseling patients about their prognosis. Moreover, recent data indicate that long-term nonadherence to DOAC therapy may be as much as 40%–70% and more severe among patients taking oral medications multiple times each day [60]. Thus, practitioners should take these challenges into consideration when determining the type and length of anticoagulation.

Special Populations

The choice of anticoagulant agent selection must be made in the context of patient-specific comorbidities. Although the DOACs have many attractive qualities over VKA and parenteral agents, they have not been extensively evaluated or are contraindicated in certain patient populations such as pregnancy, cancer, antiphospholipid syndrome (APLS), heparin-induced thrombocytopenia (HIT), renal impairment, obesity, liver impairment, and pediatrics. The following section addresses each of these specific conditions.

Pregnancy and Lactation

Pregnant patients should avoid DOACs as they may cross the placenta, and none have been adequately investigated for efficacy or fetal safety [35, 47]. Furthermore, there is evidence that they are present in breast milk. Whether this is harmful to the infant is currently unknown. For these reasons, DOACs should not be used during pregnancy or breastfeeding. LMWH is the recommended agent for pregnant patients.

Cancer

The treatment of patients with active malignancy and VTE can be challenging. Cancer patients are two to six times more likely to suffer hemorrhagic complications during VTE treatment than noncancer patients. These patients also have an additive risk of re-thrombosis associated with antineoplastic therapy and an excessive risk of treatment failure with standard anticoagulation. Until recently, guidelines recommended LMWH for the treatment of VTE in oncology patients. A meta-analysis of 10 studies within the phase III trials of apixaban, dabigatran, edoxaban, and rivaroxaban found that DOACs were as effective and safe as conventional treatment (VKA) for the prevention of VTE in patients with cancer. However, these DOAC trials included too few oncology patients to change guideline recommendations and were compared to VKA which was shown to be inferior to LMWH in previous trials [61, 62]. Recent trials indicate that, at least in the short term, edoxaban (Hokusai) and rivaroxaban (Select-D) resulted in similar to lower rates of recurrent VTE or VTE-related deaths compared to standard anticoagulation with dalteparin [63, 64]. However, both agents were associated with higher rates of bleeding and, in particular, gastrointestinal (GI) and genitourinary (GU) bleeding. These two studies led to a change in the American Society of Clinical Oncology clinical practice guidelines which now include both rivaroxaban and edoxaban as possible therapies for cancer-related thrombosis; however, the guidelines caution their use in patients with high risk for mucosal bleeding including GI and GU cancers and to check for any drug–drug interactions prior to their use [65]. Shortly after these guidelines were released, the ADAM VTE trial investigated the use of apixaban as compared to LMWH in cancer patients and demonstrated significantly fewer major bleeds in the apixaban arm versus the LMWH arm as well as less recurrent VTE [66]. This study involved only 300 patients which is in contrast to the Select-D and Hokusai studies, which included over 400 and 1000 patients each, respectively. A fourth and larger apixaban versus LMWH study, Caravaggio, recently enrolled over 1000 cancer patients with VTE, and results are pending [67]. Given these data, clinicians should carefully review the pros (decreased risk of VTE) and cons (increased risk of bleeding) surrounding the use of DOACs in cancer patients with VTE and make a decision on the type of anticoagulation through shared decision-making. Importantly, the DOACs have not been extensively evaluated in patients with primary or secondary brain metastases, and studies in these populations are much needed. Additionally, patients with ongoing bleeding issues, need for frequent procedures, and concurrent use of CYP3A4 or P-glycoprotein may benefit from remaining on LMWH.

Antiphospholipid Syndrome (APLS)

Available data draw into question whether DOACs are effective or safe in patients with antiphospholipid syndromes. Several studies suggest that the DOACs are less effective than warfarin in preventing recurrent VTE, especially in those patients

who are considered high risk, including those with arterial thrombosis and those who test positive for all three antiphospholipid antibodies. The largest meta-analysis of 47 studies representing 447 patients found that 16.9% of patients who received an FXa inhibitor developed recurrent thromboses [68]. Additionally, patients with triple positivity (positivity for all three antiphospholipid antibodies assays) had a four-fold increased risk of recurrent thrombosis as compared to warfarin. The most recent study, the Trial on Rivaroxaban in AntiPhospholipid Syndrome (TRAPS), which evaluated the use of rivaroxaban in high-risk APLS patients (defined as triple-positivity) was stopped early as it demonstrated an increased rate of events (thrombosis, major bleeding, or vascular mortality; 22% vs. 3%; HR 7.4; 95% CI 1.7–32.9; P = 0.008) with rivaroxaban compared to warfarin, hence showing no benefit and excess risk [69]. Thus, DOACs do not appear to be effective or safe in APLS patients and, therefore, warfarin remains the recommended anticoagulant. Randomized controlled trials evaluating the efficacy and safety of DOACs in patients with triple positivity as well as in APLS subgroups are presently underway.

Heparin-Induced Thrombocytopenia (HIT)

The current recommended treatment for patients with HIT is argatroban as it does not cross-react with HIT antibodies. However, its use is limited by cost, bleeding risk, and need for IV administration. Fondaparinux is also a treatment option, and although widely used in practice, it is not FDA approved for this condition. The DOACs are structurally unrelated to heparin and studies have found, for example, that apixaban does not activate platelets in the presence of HIT antibodies [70]. Furthermore, several case reports have demonstrated that DOACs are successful in treating patients with proven HIT [71, 72]. Recently, the American Society of Hematology released guidelines for the diagnosis and treatment of HIT, and DOACs are included in the suggested therapy options with the caveat that this is a conditional recommendation with very low certainty in the evidence about effects [72]. Thus, further investigations exploring the safety and efficacy of apixaban for the treatment of HIT are warranted.

Renal Impairment

Patients with VTE who are also in renal failure can be challenging to treat. UFH is the preferred parenteral anticoagulant in patients presenting with PE and severe renal dysfunction, due to its predominately nonrenal metabolism [73]. LMWH and fondaparinux are renally eliminated, and accumulation of anti-Xa activity is expected to occur and may necessitate dose reductions (Table 1) [74]. Both agents should be avoided in patients with end-stage renal disease or on renal replacement therapy. [75, 76]. Anti-Xa trough monitoring may be warranted in patients with

severe renal impairment to ensure that therapeutic targets are achieved. While argatroban and bivalirudin are both minimally eliminated in the urine, data suggest that an initial dose reduction is required for bivalirudin based on the degree of renal impairment. [22, 49, 77–82]. Alterations in PK/PD of warfarin in the setting of kidney disease are not well established; however, lower doses, greater fluctuations in INR results, and higher risk of bleeding have been reported, and thus, close monitoring is warranted [83].

All DOACs are eliminated through the kidney to varying degrees, and therefore, bleeding risk may increase with worsening renal function (Table 2) [29–32]. DOACs should be used with caution in patients with significant renal dysfunction as limited data exist regarding their use in patients with creatinine clearance ≤15–30 mL/min. However, some data, albeit limited, exist and are most robust for apixaban [84]. While increased area under the receiver operating characteristics [ROC] curve (AUCs) have been observed in patients with chronic kidney disease (CKD) taking apixaban [29, 83], data suggest that these increases may not be clinically important with regard to apixaban safety and effectiveness. Despite FDA-approved rivaroxaban use in patients with a CrCl 15–30 mL/min, limited data are available to support the safety and efficacy of rivaroxaban use in patients with severe renal impairment and caution is advised [32]. Dabigatran undergoes significant renal elimination compared to other DOACs available, and despite being associated with a reduced risk of stroke or systemic embolism, it was associated with a significant increased risk of bleeding and hemorrhagic death in patients with CKD [7].

Hepatic Impairment

Altered hemostasis in liver disease can make anticoagulation management particularly challenging in the setting of coagulation factor defects, thrombocytopenia, increased fibrinolysis, and prothrombotic changes [85]. This risk is compounded by increased risk of systemic bleeding, including variceal bleeding, and thrombosis in this patient population. Chronic liver disease may falsely elevate PTT and INR, leading to confusion over interpretation of these results in patients on IV UFH or VKA [85]. Anti-Xa values for heparinoid monitoring may be used; however, these tests have not been validated in patients with hepatic disease [73]. LMWH may be advantageous compared to UFH in the setting of hepatic disease due to its fixed, weight-adjusted dosing. However, when utilizing LMWH, close monitoring is warranted as renal function may be overestimated in this patient population [73]. Fondaparinux is predominately renally eliminated; however, limited data are available to provide guidance on the safety and efficacy of fondaparinux in patients with hepatic dysfunction [21].

Bivalirudin is unaffected by hepatic impairment and, therefore, can be used in these patients [22]. Alternatively, argatroban should be used with caution in patients with moderate-to-severe hepatic impairment (Child–Pugh class B or C), and if needed, a reduced dose is recommended [24, 77, 86]. Warfarin has historically been

the treatment of choice for oral anticoagulation in patients with liver disease [87]. However, in patients with abnormal baseline coagulation parameters, alternative anticoagulant agents should be considered [73]. All DOACs undergo varying degrees of hepatic metabolism (Table 2) and are not recommended for use in patients with Child–Pugh class C [29–32]. Additionally, edoxaban and rivaroxaban are not recommended in moderate hepatic impairment (Child–Pugh class B), and there are insufficient data for dabigatran and apixaban in these patients, thus should be used with caution [29–32, 88].

Obesity

Physiologic changes that occur in obesity can alter the PK/PD properties of medications. These alterations include increased body mass with disproportional increases in lean and adipose tissue, increased cardiac output and blood volume, increased glomerular filtration rate, and altered hepatic metabolism and hepatic blood flow [89, 90]. FDA labeling does not currently recommend dose adjustments for patients with extreme obesity [19, 21, 29–32, 74].

Weight-based dosing is particularly challenging in obese patients receiving heparin due to the unpredictable PK and interpatient variability in dose response [91]. Weight has been reported to be the best predictor of an individual response to IV UFH, and weight-based dosing regimens based on total body weight (TBW) were superior to dosing based on ideal body weight [92]. In patients receiving IV UFH, using adjusted body weight (AdjBW) in obese patients resulted in similar times to therapeutic PTT and adverse events compared to nonobese patients dosed by total body weight (TBW) [91]. Current guidelines recommend that IV UFH dosing should be based on either TBW or AdjBW [75]. Empiric dose capping may increase risk of under anticoagulation in obese patients and is not recommended.

Current controversy exists on whether dosing enoxaparin based on TBW in obese patients may contribute to supratherapeutic levels and increase bleeding risk. Capping, modifying doses, or dosing based on AdjBW has been proposed as possible dosing strategies, but further investigation is needed [76]. A trend toward increased VTE recurrence was observed in obese patients receiving enoxaparin 1.5 mg/kg SQ q24h compared to 1 mg/kg SQ q12h and, thus, should be avoided [38]. In patients with a BMI $\geq$ 40 kg/m^2, the dose of enoxaparin required to achieve therapeutic anti-Xa ranged from 0.59 to 1 mg/kg, with a median dose of 0.74 mg/kg in one study [93]. Dosing 0.75 mg/kg TBW in morbidly obese patients with a BMI $\geq$ 40 kg/m^2 was further supported by a subsequent cohort study [94]. Currently, twice-daily enoxaparin, using TBW, is recommended over once daily dosing, and dose capping is not advised [75]. Further large-scale studies are required to determine if enoxaparin 0.75 mg/kg twice daily dosing is superior to standard dosing in the morbidly obese patients.

On subgroup analyses of the MATISSE trial, 11% patients weighing >100 kg and 28% had a BMI ≥ 30 kg/m^2 who received fondaparinux 10 mg subcutaneously once daily did not have an increased risk of VTE recurrence or major bleeding compared to those who were not obese [95]. While patients with BMI ≥ 50 kg/m^2 were included, the numbers were too small to evaluate for differences in outcomes and caution is advised in using fondaparinux in morbidly obese patients. Current data suggest that both argatroban and bivalirudin should be dosed using TBW in obese patients with HIT [96–99]. Caution is advised when dosing argatroban and bivalirudin in patients with BMIs >51 kg/m^2 and >56 kg/m^2, respectively, as trials only enrolled patients below these weights.

Few patients with significant obesity were included in the DOAC trials, and their efficacy in relationship to body weight and percent body fat content remains unknown. Subsequently, the International Society of Thrombosis and Hemostasis suggests that DOACs should not be used in patients with a BMI > 40 kg/m^2 or TBW > 120 kg due to limited data [100]. If DOACs are used, clinicians may consider drawing drug-specific peak and trough levels to ensure that they fall within expected range. In the absence of robust data, PK/PD studies have augmented clinical decision-making for DOAC agent selection.

While a moderate number of obese patients were included in the larger clinical trials evaluating DOAC efficacy and safety, inconsistencies across studies and variations in weight cutoffs limit interpretation of their utility in the morbidly obese population [4, 6, 7, 51, 54]. A large retrospective database assessing the impact of obesity included 3432 patients, of which >30% were considered obese with 2.9% patients having a BMI > 40 kg/m^2, found that a high BMI was not associated with inferior DOAC safety or effectiveness in the treatment of VTE or atrial fibrillation [101]. Given the current available evidence, rivaroxaban and apixaban are likely safe and efficacious in patients weighing ≤120 kg or BMI ≤ 40 kg/m^2 [102]. There are limited data in patients above these cutoffs and caution is advised. Similarly, patient weight <50 kg was not adequately represented in the DOAC clinical trials, and therefore, the safety and efficacy of DOACs in this population is also not known and their use should be avoided. The one exception is edoxaban, which can be dose reduced in patients <60 kg.

In addition to the complexities associated with obese patients and the use of oral anticoagulants, those who undergo bariatric surgery pose additional challenges. The anatomical changes that occur in patients undergoing bariatric surgery may significantly alter absorption and, thus, require careful selection of anticoagulation agents to ensure optimal safety and efficacy [103]. The reduction in caloric intake or patients on restrictive diets may reduce rivaroxaban bioavailability. VKA resistance may be observed if significant resection of stomach and proximal small intestine occurs; however, many patients may experience enhanced sensitivity after surgery and require decreased dosages [103]. If DOACs are utilized after bariatric surgery, preference should be given to the agent whose primary absorption site was not

impacted by surgery (Table 2). Clinicians may consider obtaining drug-specific peak and trough level monitoring [103].

Pediatrics

While there are no FDA-approved anticoagulants in the pediatric population, the mainstay of VTE treatment has been UFH, LMWH, or warfarin therapies [104]. Targeted pediatric evidence with DOACs is starting to emerge, though much of the historic evidence for VTE treatment is limited and extrapolated from adult patients [105–107].

Anticoagulation Reversal

By nature, all anticoagulants are associated with an increased risk of bleeding, and anticoagulation reversal may be clinically indicted in patients presenting with symptomatic hemorrhage. Available agent-specific reversal agents are described in Table 4. UFH may be fully reversed by administration of protamine sulfate whereby only partial reversal of LMWH occurs [108]. While no specific antidote exists for fondaparinux reversal, recombinant factor VIIa or activated prothrombin complex has reversed anticoagulant effects of fondaparinux in vitro [108]. No specific reversal agents are available for parenteral DTIs. VKA may be reversed with administration of vitamin K; however, the onset of action for reversal may be unacceptably long [108]. Thus, in major hemorrhage, 4-factor prothrombin complex concentrate (4F-PCC) or fresh-frozen plasma may be administered to immediately reverse the effects of the VKA, while vitamin K is concurrently administered to maintain reversal effects [108]. 4F-PCC is superior to fresh-frozen plasma (FFP) for VKA reversal and achievement of effective hemostasis, rapid INR reversal, and should be utilized when available [109, 110]. Andexanet alfa is FDA approved for reversal of apixaban and rivaroxaban. Off-label use of 4F-PCC has historically been used in this setting and may be indicated if andexanet alfa is unavailable [111]. Idarucizumab is FDA approved for reversal of dabigatran and typically administered as a one-time bolus, though repeat dosing has been reported in the setting of massive dabigatran accumulation [112].

Table 4 Reversal of therapeutic anticoagulation [108, 118–121]

	Protamine sulfate	Vitamin K	Prothrombin complex concentrate	Fresh-frozen plasma	Idarucizumab	Andexanet alfa
Anticoagulant reversed	UFH (complete) LMWH (partial)	VKA	VKA Apixaban, rivaroxaban, edoxaban	VKA	Dabigatran	Rivaroxaban, apixaban
Mechanism of action	Neutralization of heparin	Synthesis of new vitamin-K-dependent coagulation factors	Replacement of vitamin-K-dependent coagulation factors	Replacement of vitamin-K-dependent coagulation factors	Humanized monoclonal antibody that binds to dabigatran and its metabolites to neutralize dabigatran effect	Modified recombinant factor Xa that binds to and sequesters factor Xa inhibitors
Dose	12.5–50 mg	1–10 mg IV/PO	25–50 units/kg or fixed dose 1500–2000 units	10–15 mL/kg	5 g IV x 1	400–800 mg IV bolus followed by 4–8 mg/min infusion for 2 hours
Onset	5 min	Initial onset: 6–10 hours (PO) or 1–2 hours (IV) Peak effect: 24–48 hours (PO) or 12–14 hours (IV)	Within minutes (warfarin reversal)	Within minutes	<5 minutes	2–5 minutes
Duration	2 hours	Patients may be resistant to warfarin up to a week after administration	6–8 hours	1.5–2 days	24 hours	4 hours

IV intravenous, *mg* milligram, *min* minute, *LMWH* low-molecular-weight heparin, *PO* per os (by mouth), *UFH* unfractionated heparin, *VKA* vitamin K antagonist

Future Directions

While anticoagulation therapy has made much headway over the past decade, there is still significant progress to be made to optimize the treatment of patients with PE. Clinicians may be reluctant to initiate DOAC therapy without receiving parenteral anticoagulant therapy first, especially in the case of extensive disease or presence of right ventricular strain [113]. Approximately 24–46% of patients enrolled in DOAC trials were noted to have extensive PE and, thus, may be at high risk of recurrent VTE [113]. A recent indirect meta-analysis of DOAC compared to heparinoid/VKA therapy, including 11,539 patients, and found that the relative risk of recurrent VTE was 0.8 (95% confidence interval [CI] 0.6–1.1) in patients with heparin lead-in and 1.1 (95% CI 0.8–1.5) in patients without heparin lead-in. Although this indirect evidence suggests a heparin lead-in before DOACs may be advantageous in PE, future studies are need to determine whether patients with extensive disease would benefit from initial parenteral therapy [113].

Select patient populations at high risk for clinical failure or hemorrhagic events, such as those who are morbidly obese, frail, elderly, or in severe kidney dysfunction, require further investigation into the optimal anticoagulation therapy that balances safety and effectiveness. Furthermore, patients managed with VKA in the outpatient setting have historically been closely monitored, as INR results are checked frequently by anticoagulation specialists. With transition to DOACs with less need for monitoring, establishment of close clinical follow-up for adherence and outcomes may still be needed. With the availability of agent-specific anti-Xa levels brings forth new questions on the utility of therapeutic drug monitoring for patients undergoing urgent procedures and presenting with clinical failure or hemorrhagic events. Finally, studies on the use of DOACs in conjunction with advanced therapies such as catheter-directed thrombolysis are also lacking and require further investigation.

Conclusion

VTE is a common disorder and is associated with significant morbidity and mortality. The acute treatment and secondary prevention of VTE have been revolutionized by the development of highly specific oral inhibitors of the coagulation cascade. Indeed, the DOACs have emerged as the treatment of choice for many patients given their convenience, predictable pharmacokinetics and pharmacodynamics, and their similar effectiveness in reducing VTE compared to VKA, with significantly less major bleeding [5, 47]. There are some populations in which DOACs are not currently recommended or their effect is unknown, with ongoing trials in these patient groups. It is essential that clinicians become familiar with the individual characteristics, dosing regimens, benefits, limitation, and associated challenges of each DOACs to ensure that they are used safely and effectively.

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Indications for Systemic Thrombolysis Over Anticoagulation

Lauren K. Stewart and Jeffrey A. Kline

Introduction and Overview

Thrombolytic agents were first used to treat pulmonary embolism (PE) over 50 years ago [1, 2]. Their general mechanism of action involves the activation of native plasminogen to plasmin, resulting in the hydrolysis of fibrin. Through this mechanism, systemic thrombolysis produces systemic fibrinolysis, leading to more rapid clot lysis, hastening the resolution of right ventricle (RV) strain from acute PE, and resulting in early hemodynamic improvement. It has been hypothesized, but not clearly demonstrated, that infusion of fibrin-specific thrombolytics in an arm vein affords a "first-pass" effect that localizes fibrinolytic action in the lung. Whether this hypothesis is true or not, the accelerated lytic effect in the lung vasculature comes at the cost of an increased risk of bleeding, which can be life-threatening. The strongest indication for systemic thrombolysis is in patients with sustained hypotension, termed high-risk PE, which predicts a >20% probability of death in the next 24 hours [3–5]. Although the data supporting the indication for fibrinolysis in this setting are limited in quantity and quality, all clinical guidelines recommend systemically administered, full-dose fibrinolysis with sustained hypotension [3, 6, 7]. The role of thrombolysis in acute PE of lesser severity is controversial.

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Thrombolytic Agents

All commercially marketed thrombolytic agents cause fibrinolysis by activating plasminogen (Fig. 1). Plasminogen is a zymogen that must be modified to have proteolytic activity on the fibrin backbone. With the exception of streptokinase

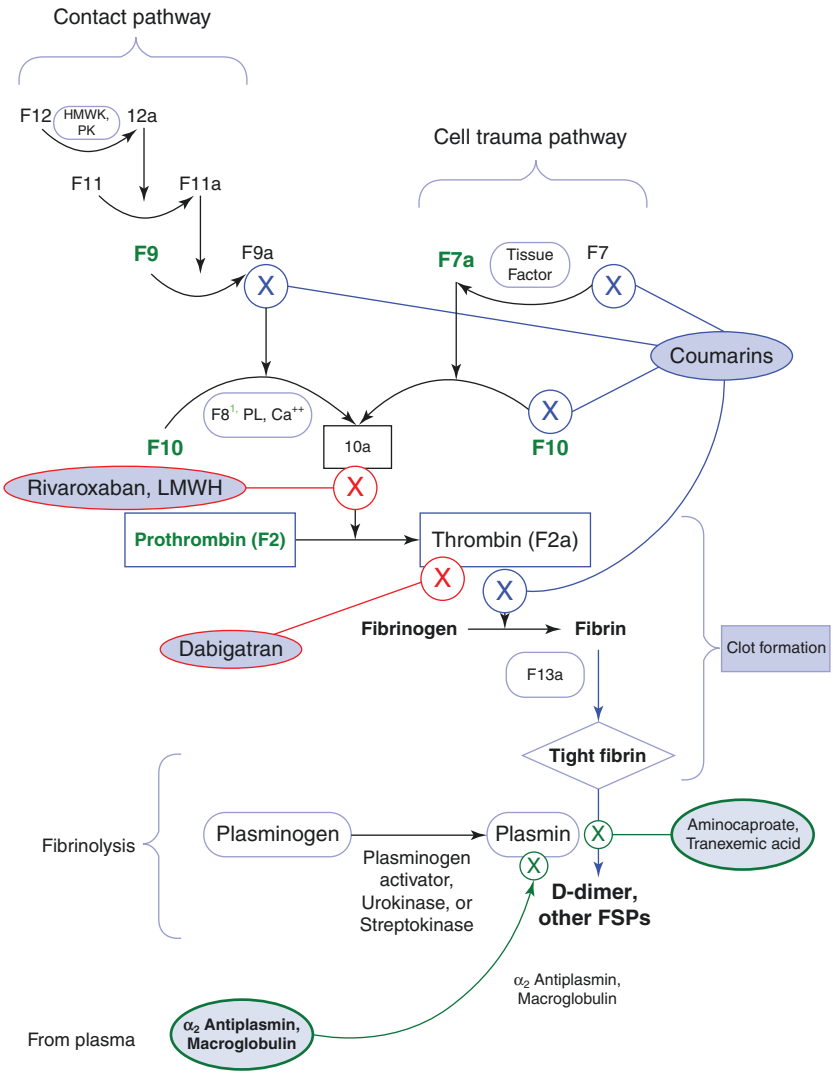

Fig. 1 Coagulation and fibrinolytic pathway summaries demonstrating the location of anticoagulant action compared with fibrinolysis. Points of inhibition are indicated by an X with a circle. (abbreviations: HMWK high-molecular-weight kininogen, LMWH low-molecular-weight heparin, PK prekallikrein, F factor)

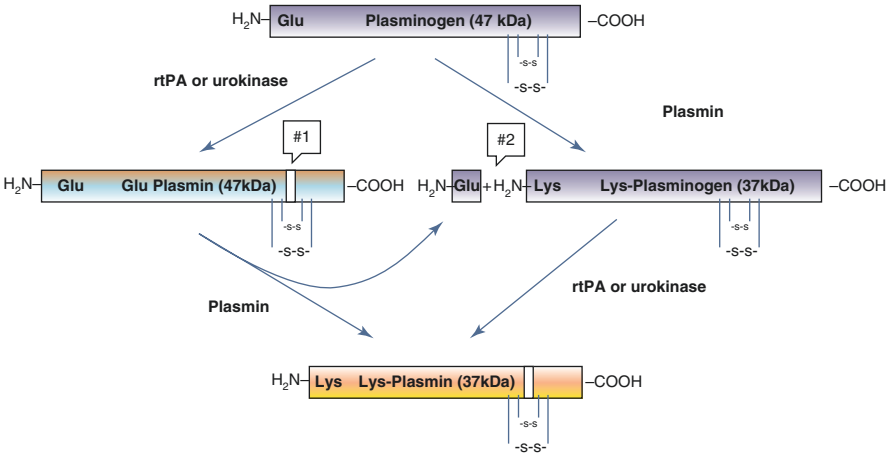

Fig. 2 Mechanism of activation of plasminogen to plasmin by fibrinolytic agents (excluding streptokinase) requires a two-step cleavage that must occur on the fibrin surface. The fibrinolytic agent [e.g., urokinase or tissue plasminogen activator (tPA)] must cleave the plasminogen in the sequence between the disulfide bonds (#1) to open the active site, and then plasmin is required to cleave at site #2 to release an N-terminal fragment to yield fully active plasmin (37 kDa)

(SK), all fibrinolytic agents covalently cleave plasminogen to form plasmin (Fig. 2), a proteolytic enzyme which then hydrolyzes insoluble fibrin contained within a thrombus into soluble polypeptides derivatives, resulting in clot lysis and a reduction of thrombus size. Streptokinase binds to plasminogen, causing a conformational change that sterically opens its serine protease active site and increases its catalytic activity several thousand folds [8–13]. The three thrombolytic agents currently cleared by the FDA with an indication for use in acute PE are alteplase (rt-PA), streptokinase, and urokinase. Tenecteplase and reteplase are genetically modified versions of rt-PA that are not cleared by the FDA for use in PE but have been used in several reports to treat this condition (Table 1) [14–16].

Alteplase

Tissue plasminogen activator (t-PA) is a naturally occurring serine protease produced by endothelial cells. Alteplase is rt-PA manufactured using recombinant DNA methods that works by covalently modifying fibrin-bound plasminogen into plasmin. The alteplase enzyme displays five curled amino acid motifs known as kringles that bind to lysine residues in fibrinogen molecules polymerized within a fibrin network. Because it requires the fibrin molecule to co-localize with plasminogen to execute its two-step cleavage to plasmin (Fig. 2), alteplase is relatively fibrin-specific and activates very little circulating systemic plasminogen. This fibrin specificity reduces unwanted digestion of soluble fibrinogen, which is an

Table 1 Comparison of thrombolytic agents

Thrombolytic agent	FDA approved for PE	Route and timing of administration	Plasma half-life (min)	Antigenic	Fibrin specificity	Generation
Alteplase	Yes	IV infusion over 2 hours	4–8	No	++	Second
Streptokinase*	Yes	IV infusion over 24 hours	12–20	Yes	–	First
Urokinase*	Yes	IV infusion over 12 hours	7–20	No	–	First
Tenecteplase	No	Single bolus injection	15–24	No	+++	Third
Reteplase	No	Two bolus injections	11–19	No	+	Third

*SK and UK no longer available in US

independent risk factor for hemorrhage [8, 11, 17]. The FDA-cleared dosing for this indication is 100 mg intravenous infusion over 2 hours. Bolus dosing has also been suggested in prior studies as an effective means of administration with the potential to reduce bleeding complications [14].

Streptokinase

Streptokinase (SK) is a bacterial polypeptide produced from beta-hemolytic streptococcus cultures. It functions by binding to plasminogen, forming a streptokinase-plasminogen activator complex that activates plasmin. SK is a first-generation thrombolytic agent that is not fibrin-specific, binding equally avidly to circulating and fibrin-bound plasminogen. Therefore, SK depletes fibrinogen concentrations more severely than alteplase. Streptokinase is antigenic and is the agent most commonly associated with adverse reactions [11, 18, 19]. The typical dosing regimen for SK is 250,000 units IV over the initial 30 minutes, followed by 100,000 units per hour for 24 hours. Despite being FDA approved for use in acute PE, prolonged dosing and relatively poor side effect profile of SK have limited its use, and it is no longer available in the United States but may be the agent of choice in tier 1 and 2 countries [14].

Urokinase

Urokinase, synthesized predominantly by the kidneys and excreted in the urine, activates plasminogen by covalent cleavage. In vivo, urokinase functions primarily as an activator of extravascular fibrinolysis in the wound repair and

remodeling process [9, 20]. Similar to SK, urokinase is a first-generation thrombolytic agent that lacks fibrin specificity. It does not, however, carry the same antigenic properties. Systemic urokinase dosing involves the administration of 4400 units/kg over the initial 10 minutes, followed by 4400 units/kg per hour for 12 hours. The overall use of urokinase is limited, and it is not currently available in the United States. Urokinase was studied in the landmark Urokinase Pulmonary Embolism Trial (UPET) in 1970, which demonstrated that while urokinase led to more complete angiographic resolution of pulmonary vascular obstruction at 24 hours, it offered no difference in mortality compared with placebo [21].

Other Agents

The third-generation plasminogen activators, reteplase and tenecteplase, have been used off-label in research protocols to treat PE. These recombinantly produced plasminogen activators contain modified amino acid sequences, designed to evade binding to the natural inhibitor of fibrinolysis, plasminogen activator inhibitor 1 (PAI-1) [22, 23]. As a result, they have longer half-lives than the previous thrombolytic agents discussed, allowing for faster administration with bolus dosing [14]. Tenecteplase was the fibrinolytic used in Pulmonary Embolism Thrombolysis (PEITHO) trial, the largest randomized, placebo-controlled trial of fibrinolysis for PE to date [16]. Patients randomized to single bolus tenecteplase in PEITHO were less likely than patients given a placebo to develop arterial hypotension. However, as with all other single trials of fibrinolysis for PE, PEITHO did not have the power to detect a difference in mortality.

Adverse Reactions

Bleeding is the most common adverse effect. It can be observed minutes to hours after administration and can range from nuisance bleeding (e.g., bleeding from puncture wounds) to catastrophic intracranial hemorrhage (ICH). Other significant adverse effects include allergic reactions and hypotension, almost exclusively observed after streptokinase administration, especially with repeated dosing. Mild reactions such as rash and pyrexia can appear in up to 10% of patients, whereas major reactions are much less common, with anaphylaxis noted in less than 0.5%. Hypotension has also been reported with SK use, particularly with faster infusion rates [18, 19, 24]. There are several case reports of angioedema and anaphylactoid reactions following alteplase administration, probably related to bradykinin production from off-target effects of alteplase on kallikrein [25]. These reactions are typically mild and self-limited [26, 27].

Summary

Alteplase (rt-PA) is typically the most preferred agent due in part to its short infusion rate and label indication for PE by the FDA. The longer infusion durations and fibrinogen-depleting properties of first-generation agents (streptokinase and urokinase) make them less convenient and limit their use. Further, agents such as alteplase, tenecteplase, and reteplase have greater fibrin specificity than first-generation agents, as they preferentially activate plasminogen on the thrombus surface rather than systemic plasminogen and may allow the first-pass effect causing preferential lung vascular fibrinolysis. Streptokinase has a greater risk of allergic reactions. Although approved by FDA for use, these first-generation agents have limited availability in the United States.

Contraindications to Thrombolytics

Systemic thrombolysis increases the risk of major bleeding, with pooled data suggesting a 10–15% frequency (Table 2), significantly higher than the 5% rate observed with placebo [28]. However, if we restrict the trials to those that used alteplase only (Table 2), the rate of intracranial hemorrhage is far smaller, at approximately 0.8%, and not different compared with placebo. Therefore, the bleeding risk for each individual patient and clinical scenario should always be carefully considered. Studies examining risk factors for bleeding after thrombolytic administration have identified several factors including recent major surgery, a prolonged prothrombin time, administration of catecholamines for systemic arterial hypotension, cancer, diabetes mellitus, and low body weight [29, 30]. A risk score has been developed to predict intracranial hemorrhage with fibrinolysis for PE, comprising peripheral vascular disease (1 point), age greater than 65 years (elderly) (1 point), prior cerebrovascular accident with a residual deficit (5 points), and prior myocardial infarction (heart attack) (1 point). Scores of 0, 1, 2, and ≥5 points were associated with ICH risks of 1.2%, 1.9%, 2.4%, and 17.8%, respectively. This score has not been independently validated [31]. Contraindications for systemic thrombolytic therapy are classified as either absolute or relative, with absolute contraindications including active bleeding, prior intracranial hemorrhage, ischemic stroke within the past 3 months, history of structural intracranial cerebrovascular disease or neoplasm, recent CNS surgery, suspected aortic dissection, and recent significant closed-head trauma [6, 7]. These contraindications are displayed in Table 3. Ultimately, the weight of these contraindications depends on the severity of the particular clinical scenario at hand, and the decision regarding thrombolytic administration should be made on a case-by-case basis.

Table 2 Major bleeding and intracranial bleeding in prospective trials

Treatment	*N*	Major bleeding rate (%)	ICH rate (%)	Reference
Urokinase 50,000 units/lb	82	32.9	NR	UPET 1970 [21]
t-PA 0.6 mg/kg	33	0	0	Levine et al. 1990 [32]
t-PA 40–80 mg	9	11.1	0	PIOPED Investigators, 1990 [33]
r-PA 20 units	23	4.3	0	Tebbe et al. 1999 [34]
t-PA 100 mg	13	7.7	0	Tebbe et al. 1999 [34]
t-PA 100 mg	20	15	NR	Dalla-Volta et al. 1992 [35]
Urokinase 3 million units	45	10.9	2.2	Goldhaber et al. 1992 [36]
t-PA 100 mg	44	15.9	4.5	Goldhaber et al. 1992 [36]
Urokinase 57,200 units/kg	29	27.6	3.4	Meyer et al. 1992 [37]
t-PA 100 mg	34	20.6	0	Meyer et al. 1992 [37]
t-PA 100 mg	46	NR	2.2	Goldhaber et al. 1993 [38]
t-PA 0.6 mg/kg	60	3.3	0	Goldhaber et al. 1994 [39]
t-PA 100 mg	27	7.4	7.4	Goldhaber et al. 1994 [39]
t-PA 0.6 mg/kg	36	8	0	Sors et al. 1994 [40]
t-PA 100 mg	17	6	0	Sors et al.1994 [40]
SK 1.45 million units	25	12	NR	Meneveau et al. 1997 [41]
t-PA 100 mg	25	16	NR	Meneveau et al. 1997 [41]
SK 1.5 million units	43	8	NR	Meneveau et al. 1998 [42]
t-PA 100 mg	23	20	NR	Meneveau et al. 1998 [42]
t-PA 100 mg	118	0.8	0	Konstantides et al. 2002 [43]
t-PA 100 mg	7	0	0	Muhl et al. 2007 [44]
SK 9 million units	8	0	0	Muhl et al. 2007 [44]
TNK 30–50 mg	525	NR	2.7	Bottiger et al. 2008 [45]
TNK 30–50 mg	28	7.1	3.6	Becattini et al. 2010 [15]
t-PA 50 mg	55	3.6	1.8	Wang et al. 2010 [46]
t-PA 100 mg	48	10.4	0	Wang et al. 2010 [46]
t-PA 100 mg	37	5.4	0	Fasullo et al. 2011 [47]
t-PA 50 mg	61	0	0	Sharifi et al. 2013 [48]
SK 2.65–5.05 million units	75	1.3	1.3	Patra et al. 2013 [49]
TNK 30–50 mg	25	0	0	Patra et al. 2013 [49]
TNK 30–50 mg	506	11.5	2.0	Meyer et al. 2014 [16]
SK 2.65–5.05 million units	105	1.9	NR	Patra et al. 2014 [50]
TNK 30–50 mg	25	0	NR	Patra et al. 2014 [50]
TNK 30–50 mg	40	2.5	2.5	Kline et al. 2014 [51]
t-PA 10–20 mg	30	0	0	Kucher et al. 2014 [52]

Table 3 Contraindications for systemic thrombolytic therapy

Relative contraindications	Absolute contraindications
Systolic blood pressure > 180 mmHg	Active bleeding
Diastolic blood pressure > 110 mmHg	Prior intracranial hemorrhage
Recent bleeding	Brain or spinal surgery within prior month
Ischemic stroke more than 3 months prior	Ischemic stroke within 3 months
Current use of anticoagulation	Suspected aortic dissection
Recent non-CNS surgery or invasive procedure	Structural cerebrovascular disease or CNS neoplasm
Traumatic or prolonged cardiopulmonary resuscitation	Recent head trauma with fracture or brain injury
Pericarditis or pericardial fluid	Abdominal surgery within 7 days
Diabetic retinopathy	
Pregnancy	
Age > 75 years	
Low body weight (<60 kg)	

Indications for Thrombolysis Based on Risk Stratification of Pulmonary Embolism

Classification and Risk Stratification

Outcomes following acute PE vary based on the severity of pulmonary vascular obstruction and its variable effect on cardiac output, patient age, and comorbid conditions. Several consensus statements and societal guidelines aid in this risk stratification (Table 5). High-risk or massive PE is generally defined as acute PE with sustained hypotension (e.g., systolic blood pressure <90 mmHg for at least 15 minutes), or a drop of at least 40 mmHg in systolic blood pressure on the same day, and signs of shock or respiratory distress. In the authors' experience, these signs may include pale and cold or cyanotic skin, diaphoresis, accessory muscle use, acute delirium, and an affect suggesting the appearance of panic. Intermediate-risk or submassive PE refers to acute PE without hypotension (systolic blood pressure always >90 mmHg) and signs of right ventricular (RV) dysfunction or myocardial necrosis. RV dysfunction has been defined as the presence of any of the following: RV dilation [apical four-chamber RV diameter divided by left ventricle (LV) diameter >0.9] or RV systolic dysfunction on echocardiography, RV dilation (four-chamber RV diameter divided by LV diameter >0.9) on CT, elevation of brain natriuretic peptide (BNP; >90 pg/mL) or elevation of N-terminal pro-BNP (>500 pg/mL). Myocardial necrosis is defined as elevation of troponin (troponin I > 0.4 ng/mL or troponin T > 0.1 ng/mL, or >14 ng/mL on high-precision troponin T measurement) [3, 6, 7, 53]. Other tools such as clinical scoring indices (revised Geneva, pulmonary embolism severity index [PESI] and simplified PESI [sPESI] scores) can aid in predicting which patients are at increased risk of adverse outcomes. The sPESI scoring criteria are included in the associated table (Table 4), with a score ≥1

Table 4 Stratification of acute PE into high, intermediate and low risk

	Hypotension (SBP <90 mmHg)	Signs of RV dysfunction or abnormal biomarkers	sPESI[a]
High risk	+	+ (although not necessary for diagnosis in presence of shock)	≥1
Intermediate risk	−	+ (presence of either criteria)	≥1
Low risk	−	−	0

[a]Score one point for each: Age >80 years, history of cancer, history of chronic cardiopulmonary disease, heart rate >110 beats per minute, systolic blood pressure <100 mmHg, oxygen saturation <90%

("high"-risk group) carrying with it an estimated 30-day mortality risk of 8.9% vs. 1.1% in those with a score of 0 ("low"-risk group) [54]. As intermediate-risk PE is a rather heterogenous group, some guidelines have proposed further stratification of this group into intermediate-low and intermediate-high-risk categories [3]. Low-risk PE is defined as normotension with no signs of RV dysfunction and normal biomarker levels. This group is associated with the lowest short-term mortality and the best overall prognosis.

Use of Thrombolytic Therapy in High-Risk Pulmonary Embolism

At least 14 systematic reviews with meta-analyses have been published since PEITHO, and one systematic review highlighted the variability in results of these in terms of effect size for mortality, bleeding risk, and recurrence rate of venous thromboembolism [55]. One persistent theme of the pooled data is that the effect sizes for survival benefits are increased for patients with persistent hypotension or cardiogenic shock from acute PE with fibrinolysis [56–67]. However, there is a paucity of large, randomized-controlled trials studying the specific use of thrombolytic therapy in hemodynamically unstable patients. Specific guidelines that recommend thrombolytic therapy in high-risk PE include those sponsored by the American Heart Association (AHA)-IIaB (moderate strength of recommendation based on moderate-quality evidence); the American College of Chest Physicians (CHEST)-2B (weak recommendation based on moderate-quality evidence); and the European Society of Cardiology (ESC)-1B (general agreement that treatment is beneficial based on moderate level of evidence) [3, 6, 7]. Thrombolytic therapy administered through a peripheral IV is often the fastest and most ideal initial approach in high-risk PE. In cases where persistent hypotension remains despite systemic thrombolysis, additional treatment modalities including catheter-directed or mechanical therapy may be considered. All patients who receive systemic or catheter-directed fibrinolysis should receive full-dose anticoagulation with heparin with a target

partial thromboplastin time between 60 and 120 seconds, which can generally be achieved with a loading bolus of 5000 units followed by 16 units/kg/hour infusion of unfractionated heparin. Low-molecular-weight heparin has also been used as the anticoagulant with thrombolysis for acute PE [51].

Use of Thrombolytic Therapy in Intermediate-Risk Pulmonary Embolism

The role of systemic fibrinolysis in intermediate-risk PE, defined as PE with evidence of RV dysfunction or myocardial necrosis without systemic hypotension, is less clear. Several recent randomized-controlled trials have investigated the use of fibrinolysis in this group. Generally, these studies have reported improved RV function and prevention of hemodynamic decompensation at the cost of increased bleeding risk and without a proven mortality benefit [4, 15, 38, 58, 61]. The PEITHO trial suggested that fibrinolysis prevented hemodynamic decompensation but at the cost of a 10-fold increased risk of hemorrhage and stroke. There was no difference in all-cause mortality or other long-term outcomes including persistent dyspnea or right ventricular dysfunction on echocardiography over a subsequent 2-year follow-up [16, 68]. Another point of agreement among the multiple meta-analyses was that the older the patient age, the higher the risk of intracranial hemorrhage. Older age may explain part of the high rate of intracranial hemorrhage observed in PEITHO, inasmuch as the mean age of participants was 66 years [16, 56]. Published guideline recommendations are displayed in the associated table (Table 5) but largely do not

Table 5 Guidelines for the use of systemic thrombolysis in intermediate-risk PE

Guidelines	Year	Recommendation
American Heart Association (AHA)	2011	Fibrinolysis may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis) and low risk of bleeding complications (*Class IIb, Level C*)
American College of Chest Physicians (CHEST)	2016	In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (*Grade 1B*). In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low-bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (*Grade 2C*)
European Society of Cardiology (ESC)	2014	Routine use of primary systemic thrombolysis is not recommended in patients not suffering from shock or hypotension (*Grade III, Level B*). Thrombolytic therapy should be considered for patients with intermediate-high-risk PE and clinical signs of hemodynamic decompensation (*Grade IIa, Class B*)

recommend fibrinolysis for routine use in intermediate-risk PE. They do, however, suggest that fibrinolysis may be considered in normotensive patients with low-bleeding risk and evidence of acute deterioration, including multiple indexes of RV dysfunction, increasing tachycardia or shock index (heart rate/systolic blood pressure), transient drops in blood pressure or respiratory insufficiency, or clinical signs of shock [3, 6, 7]. It is important to consider that intermediate-risk PE represents a largely heterogeneous group with a wide spectrum of disease severity, precluding a "one-size-fits-all" approach. More data are needed to further elucidate which patients may be most likely to benefit from thrombolytic therapy. Ultimately, the use of thrombolysis in intermediate-risk PE should be approached on a case-by-case basis, with careful consideration of the individual clinical scenario and bleeding risk.

Use of Thrombolytic Therapy in Low-Risk Pulmonary Embolism

Thrombolysis is not recommended for treatment in low-risk PE as the risk of harm clearly outweighs any potential benefit in this group [3, 6, 7].

Other Considerations

Low-Dose Thrombolysis

Prior studies have suggested reduced-dose tPA administered in an upper extremity vein as a safer and effective treatment option in acute PE [46, 48, 62, 69, 70]. As a contextual point, it is important to note that no trial has been conducted specifically to determine the optimal dose of tPA for PE. The use of half-dose alteplase (50 mg infused over 2 hours) is most appealing in patients at higher risk of intracranial hemorrhage, such as patients of lower body weight (<50 kg), the elderly (age >65 years), pregnant patients, and those with other relative contraindications to thrombolysis. A systematic review of three randomized trials has suggested a lower bleeding rate with half-dose tPA, with no difference in mortality or efficacy endpoints including improvement in RV dysfunction and lung perfusion defects [62]. One large claim-based study employed propensity matching to compare outcomes of 548 patients (per group) treated with half-dose (50 mg) vs. full-dose (100 mg) tPA in acute PE and found an increased need for treatment escalation in the half-dose group. Hospital mortality and bleeding rates did not differ significantly [70]. Although data appear promising, evidence remains limited and further investigation is needed to determine the optimal dosing of tPA that will cautiously balance its safety and efficacy.

Catheter-Directed Thrombolysis

Catheter-directed thrombolysis (CDT) has been proposed as an alternative treatment to systemic thrombolysis that may improve safety due to its use of lower doses of thrombolytic medication. The Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) trial is the only randomized-controlled trial that has compared ultrasound-assisted CDT for acute intermediate-risk PE with heparin anticoagulation. The ULTIMA trial randomized 59 patients with an RV/LV ratio >1.0 on echocardiography to CDT (10–20 mg tPA over 15 hours) vs. heparin alone. Investigators found CDT to be superior in reducing RV dilatation, reporting a significant difference in the change in RV/LV ratio from baseline to 24 hours in the CDT vs. heparin group (0.30 vs. 0.03, $p < 0.001$) [52]. Several systematic reviews with meta-analyses have convincingly shown that CDT (with or without acoustic enhancement) is associated with a temporal reduction in RV: LV ratio and pulmonary arterial pressures [71–74]. More recently, the Optimum Dose and Duration ofAcoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism (OPTALYSE PE) trial demonstrated that even lower CDT infusion regimens (tPA dose ranging from 4 to 12 mg per lung and infusion duration from 2 to 6 h) achieve satisfactory reductions in pulmonary arterial pressure and RV:LV ratio with a low major bleeding rate [75]. The most recent CHEST guidelines recommend systemic thrombolytic therapy over CDT in routine use. However, the guidelines do suggest CDT in hypotensive patients with acute PE who have a higher-bleeding risk or have already failed systemic thrombolysis (Grade 2C) [7]. Catheter-based therapy is discussed in greater detail elsewhere.

Cardiopulmonary Arrest

Retrospective and case report data have suggested a possible role for thrombolysis in cases of cardiac arrest due to suspected or known PE [45, 76–79]. One study retrospectively examined the use of thrombolysis in cardiac arrest patients with confirmed PE, finding a higher rate of return of spontaneous circulation (ROSC) in those treated with 100 mg of tPA [81% vs. 43%, $p = 0.03$]]. Only 2 of these 21 arrest patients treated with tPA survived to hospital discharge [78]. Another study reported outcomes of 23 patients with pulseless electrical activity (PEA) and cardiopulmonary arrest due to confirmed massive PE. All patients received 50 mg of tPA as an IV push during ongoing cardiopulmonary resuscitation (CPR), with ROSC achieved in 22 of 23 patients [79]. However, multiple studies of patients with cardiac arrest of unknown etiology have found no evidence of beneficial effect of fibrinolysis, with no difference in ROSC or survival to hospital discharge [45, 76]. Overall, limited data preclude any consensus recommendation for or against use in cardiac arrest, and this decision is best made on a case-by-case basis. Thrombolysis may be reasonable to attempt in arrest due to presumed PE but likely lacks benefit in

undifferentiated arrest. If thrombolysis is attempted, most guidelines suggest an IV bolus dose of 50–100 mg of tPA.

Impact of Thrombolysis on Long-Term Outcomes

Mortality

As previously described, the results from the 14 recent systematic reviews with meta-analyses examining the impact of thrombolysis on mortality have been mixed [56–67]. Marti et al. found a significant reduction in overall mortality (OR 0.59, 95% CI 0.36–0.96) across a pooling of 15 trials involving 2057 patients [58]. However, when studies of high-risk PE were excluded from the analysis, this apparent reduction in mortality was no longer significant. Chatterjee et al. compared all-cause mortality in patients receiving thrombolytics vs. standard anticoagulation across 16 trials comprising 2115 patients. The use of thrombolytics was associated with lower all-cause mortality (OR 0.53, 95% CI 0.32–0.88), and this difference remained significant when assessed in a subgroup of 1775 intermediate-risk patients (OR: 0.48, 95% CI: 0.25–0.92). There was no significant mortality benefit in patients over 65 years treated with thrombolytics [56]. Several additional meta-analyses have demonstrated no difference in overall mortality [4, 61]. It is important to consider the methodology of these meta-analyses, as the pooling of data leads to significant heterogeneity across the dataset, with studies varying on the severity of PE and type of thrombolytic agent used, as well as its dosing, timing, and route of delivery. Long-term follow-up (median 37.8 months) from the PEITHO study demonstrated no difference in long-term survival between those treated with tenecteplase vs. placebo, with respective overall mortality rates of 20.3% and 18.0% ($p = 0.43$) [68].

Hemodynamics and RV Function

The presence of RV dysfunction in acute PE is associated with poorer outcomes, with an RV: LV ratio >1.0, increasing the probability of PE-related death five-fold [80, 81]. Systemic fibrinolysis has been shown to hasten the resolution of RV strain from PE, improving pulmonary arterial pressures, pulmonary perfusion, and RV function in the short term. Goldhaber et al. found hemodynamically stable patients treated with alteplase to have a significant improvement in both RV hypokinesis and pulmonary perfusion at 24 hours compared to those treated with heparin alone [38]. Becattini similarly reported a significant decrease in RV dysfunction (defined as an RV: LV ratio >1.0) at 24 hours in patients treated with tenecteplase vs. placebo [15]. Despite the immediate improvement in RV function afforded by fibrinolysis, contradictory data exist as to whether this benefit is preserved in the long term. Persistent

RV dysfunction is associated with negative long-term outcomes including persistent dyspnea, exercise intolerance, fatigue, and a low perception of wellness. This "post-PE syndrome" is common, afflicting as many as 30–40% of patients surviving acute PE [82]. Whether treatment with fibrinolysis affords a protective effect over this "post-PE syndrome" has been studied with inconsistent results. A recent systematic review and meta-analysis demonstrated that fibrinolysis confers long-term improvement in outcomes associated with RV function and functional capacity, assessed with the six-minute walk test [83]. However, this review did not include the longer-term secondary analysis of the PEITHO trial that found no difference in persistent dyspnea and RV dysfunction in those treated with tenecteplase [68].

Venous Thromboembolism Recurrence

Recurrent VTE often carries a heavy health burden, increasing the risk of mortality, the likelihood of CTEPH, and the duration of anticoagulation therapy, while decreasing patient quality of life [82, 84, 85]. Several meta-analyses have explored whether the use of thrombolytics has an impact on the overall rate of recurrence after acute PE, with results suggesting lower VTE recurrence in patients treated with thrombolysis [56, 58, 61].

Bleeding

The net clinical benefit of thrombolytic therapy in PE is lessened due to the increased risk of major bleeding associated with its use, with ICH being the most dreaded complication. Reported rates of ICH in patients treated with systemic thrombolysis range from 0% to 7.4%, compared with the 0–33% range in frequency of major bleeding [28]. Data from pooled studies directly comparing fibrinolysis vs. standard anticoagulation alone demonstrated a significantly increased risk of major hemorrhage and ICH in those treated with thrombolysis. Predictors of major hemorrhage following fibrinolysis and specific contraindications to be considered prior to thrombolytic administration are discussed earlier in this chapter.

Summary

In summary, systemic fibrinolysis leads to rapid clot lysis, hastening the resolution of RV strain from acute PE, and resulting in early hemodynamic improvement. However, this apparent benefit comes at the cost of an increased risk of bleeding, which can be life-threatening. Guidelines generally agree that the benefit of thrombolysis outweighs the risk in hypotensive patients with high-risk PE. Systemic

thrombolysis is not recommended for routine use in intermediate-risk PE, although it may be considered in cases where there is evidence of acute decompensation. More research is needed to further elucidate which patients in the heterogeneous "intermediate-risk" category are most likely to benefit from thrombolytic therapy.

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Endovascular Techniques in the Treatment of Acute PE

Phillip L. Guichet and Akhilesh K. Sista

Introduction to Catheter-Directed Therapy

In the event traditional therapies like anticoagulation and systemic thrombolysis are contraindicated or deemed insufficient in the treatment of a patient with acute pulmonary embolism (PE), escalation of care may call for the use of minimally invasive, image-guided endovascular therapies. The endovascular techniques used to remove, macerate, and dissolve acute pulmonary emboli (PE) are known collectively as catheter-directed therapy (CDT) [1]. CDT includes mechanical techniques such as clot fragmentation and aspiration thrombectomy, as well as pharmacological techniques like the targeted infusion of a thrombolytic agent via a multi-sidehole catheter. The goal of CDT in the treatment of acute PE is to debulk the thromboembolic load in the pulmonary vasculature, relieve life-threatening right heart strain, and improve pulmonary perfusion. This approach may improve short-term outcomes in patients with acute PE, though its effects on mortality, clinical deterioration, and the long-term sequelae of PE are unknown. This chapter will focus on the rationale for CDT in acute PE, the literature examining its use, and periprocedural management.

Role and Rationale for Catheter-Directed Therapy

The rationale for CDT varies depending on where a patient with acute PE falls within the PE risk stratification schema. As outlined in Chapter "Risk Stratification of Acute PE,", risk stratification for acute PE is based on individual patient factors,

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cardiopulmonary status, and imaging and laboratory findings. As outlined in Chapters "Treatment for Pulmonary Embolism: Anticoagulation Selection and Duration" and "Indications for Systemic Thrombolysis Over Anticoagulation," mainstay therapy in acute PE is therapeutic anticoagulation and treatment escalation with systemic thrombolysis is recommended for patients with high-risk PE and can be considered for patients with intermediate-risk PE who are at risk for clinical deterioration.

CDT, and other more aggressive clot-removal strategies like surgical embolectomy (see Chapter "Role of surgical embolectomy and ECMO in PE"), can be considered in patients with high-risk PE with continued or worsening cardiopulmonary deterioration despite systemic thrombolysis [2–4] and in patients deemed at risk of imminent death who cannot wait for systemic thrombolysis to take effect [3]. In such cases of high-risk/massive PE, patient mortality ranges from 25% to 65% and death often occurs within 1 hour of presentation [5–7]. In these patients, the goal of CDT is rapid debulking of central occlusive thrombus—in effect downstaging high-risk to intermediate-risk PE—relieving pulmonary hypertension, resolving life-threatening right heart strain, and improving pulmonary perfusion.

CDT can also be considered for patients with high- and intermediate-high risk PE with contraindications to systemic thrombolysis or for patients with a high risk of bleeding [2–4]. It is estimated that half of patients with acute PE have contraindications to systemic thrombolysis [8]. Further, systemic thrombolysis carries major risks even in carefully selected patients, with reported rates of major hemorrhage between 9% and 20% and intracranial hemorrhage between 1.5% and 3.0% [7, 9–12]. These high bleeding risks are challenging to reconcile with the low 2–3% 90-day mortality seen in intermediate-risk/submassive PE treated with anticoagulation alone [13, 14]. Physicians are therefore reluctant to escalate therapy with systemic thrombolysis. The goal of CDT for submassive PE is to achieve the therapeutic efficacy of systemic thrombolysis with less bleeding.

In theory, peripherally administered thrombolytic agents are subject to a phenomenon of fluid dynamics called the "Venturi effect," whereby eddy currents created by obstructing thrombus prevent the thrombolytic agent from contacting the clot. These vortices shunt the thrombolytic agent preferentially into unobstructed blood vessels, permitting only a fraction of the administered dose to interact with its intended therapeutic target [15]. This principle holds true even for a thrombolytic agent infused within the pulmonary artery proximal to the target thrombus [16]. CDT averts this limitation of systemic therapy by delivering the thrombolytic agent directly into the clot via a multisidehole catheter that has been placed within the obstructing thrombus under image guidance. With this targeted means of delivery, modern CDT protocols require one-fourth the dose of a thrombolytic agent (e.g., 20–24 mg alteplase) used in routine systemic thrombolysis. Further, in patients with contraindications to thrombolytic therapy who are decompensating or are at high risk of decompensating, pharmacologic CDT can be foregone in favor of mechanical clot maceration, fragmentation, and removal. Thus, CDT has the potential to achieve therapeutic success with lower overall doses of thrombolytic agent than those used in systemic thrombolysis [1].

Evidence for Catheter-Directed Therapy

The first large meta-analysis evaluating modern CDT for massive PE was published by Kuo et al. in 2009. Evaluating 594 patients, this study had a pooled clinical success rate of 86.5% (defined as stabilization of hemodynamics, resolution of hypoxia, and survival to hospital discharge) with a rate of major procedural complications of 2.4% [17]. While these data are promising, it should be noted that 500 patients in the analysis came from retrospective studies, as there are no randomized trials of CDT for high-risk PE. Since then, four prospective clinical trials have subsequently evaluated the utility of CDT in acute massive and submassive PE: the ULTIMA trial (*Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism*), the SEATTLE II trial (*A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism*), the PERFECT registry (*Pulmonary embolism response to fragmentation, embolectomy, and catheter thrombolysis: initial results from a prospective multicenter registry*), and the OPTALYSE PE trial (*A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism*). The pertinent details and results of these prospective clinical trials are summarized in Table 1 [18–21].

The ULTIMA trial was a randomized controlled trial comparing CDT to heparin alone in 59 patients with acute intermediate-risk PE. It showed that CDT was superior in reducing right ventricular dilation at 24 hours (assessed by the RV/LV ratio with echocardiography) with no increase in bleeding complications [18]. The SEATTLE II trial was a single-arm, multicenter trial assessing CDT in 119 patients with intermediate-risk PE and 31 patients with high-risk PE and concluded that CDT was associated with reduced right ventricular dilation (RV/LV ratio on CT angiography) and pulmonary artery systolic pressure at 48 hours [19]. The PERFECT registry was a single-arm, multicenter trial assessing CDT in 73 patients with intermediate-risk PE and 28 patients with high-risk PE, concluding that CDT is associated with improved right ventricular function, reduced pulmonary artery pressure, and reduced pulmonary artery clot burden [20]. The PERFECT registry did not find a clinical difference between standard CDT and ultrasound-facilitated CDT, though it was not designed or powered to compare the two techniques. Finally, OPTALYSE PE was a randomized trial comparing four novel tPA infusion protocols during CDT in 101 patients with intermediate-risk PE. It concluded that CDT utilizing lower doses of tPA and shorter infusion times was associated with reduced right ventricular dilation at 48 hours (RV/LV ratio on CT angiography) [21].

While no fatal or intracranial hemorrhage events occurred in the ULTIMA trial, SEATTLE II trial, and PERFECT registry, two episodes of intracranial hemorrhage occurred in OPTALYSE PE—one of which was attributed to CDT [21]. The intracranial hemorrhage event deemed attributable to CDT occurred in a patient randomized to the treatment arm with the most aggressive tPA dosing, notably greater than the doses used in the ULTIMA and SEATTLE II trials, and that treatment arm was thereafter discontinued. The other episode of intracranial hemorrhage in OPTALYSE

Table 1 Summary of prospective clinical trials evaluating catheter-directed therapy for acute pulmonary embolism

Trial, design	CDT regimen(s); [target thrombolytic dose]	Results	Shortcomings
ULTIMA, 2014			
Prospective, randomized trial CDT + UFH vs. UFH 59 pts with acute intermediate-risk PE	CDT × 15 h; tPA 1 mg/h/lung × 5 h, then tPA 0.5 mg/h/lung × 10 h; [10–20 mg tPA]	• Reduced RV dilation at 24 hours in the CDT arm compared with the UFH arm • Improved RV systolic function at 24 hours • No major bleeding events, no increase in bleeding	• Small sample size • Only assessed USCDT
SEATTLE II, 2015			
Prospective, multicenter trial CDT + UFH (single-arm) 119 pts with acute submassive PE 31 pts with acute massive PE	CDT ≤ 24 h; tPA 1 mg/h/lung × 24 h (unilateral PE), or tPA 1 mg/h/lung × 12 h (bilateral PE); [24 mg tPA]	• Reduction in RV dilation at 48 hours • Reduction in PA pressure at 48 hours • Decreased PA angiographic obstruction at 48 hours • 10% major bleeding; No fatal hemorrhage or ICH	• No comparator group • Only assessed USCDT
PERFECT, 2015			
Prospective, multicenter registry CDT + UFH (single-arm) 73 pts with acute submassive PE 28 pts with acute massive PE	CDT up to 24 h; tPA 0.5–1.0 mg/h/lung, or urokinase 100,000 IU/h/lung; [24 mg tPA; 2.4 × 10^6 IU urokinase]	• Reduction in RV dilation • Reduction in PA pressure • No difference in USCDT vs. standard CDT • No major bleeding events	• No comparator group
OPTALYSE PE, 2018			
Prospective, multicenter trial Compared novel CDT protocols 101 pts with intermediate-risk PE	1: CDT × 2 h; tPA 2 mg/h/lung; [4–8 mg tPA] 2: CDT × 4 h; tPA 1 mg/h/lung; [4–8 mg tPA] 3: CDT × 6 h; tPA 1 mg/h/lung; [6–12 mg tPA] 4: CDT × 6 h; tPA 2 mg/h/lung; [12–24 mg tPA]	• Reduction in RV dilation with lower doses of tPA and shorter infusion times • 4% major bleeding; 2% ICH (Two ICH events, one attributed to CDT in Arm 4)	• No non-CDT comparator • Only assessed USCDT

NB: *CDT* catheter-directed therapy, *UFH* unfractionated heparin, *PE* pulmonary embolism, *tPA* tissue plasminogen activator, *RV* right ventricle, *USCDT* ultrasound-facilitated CDT, *PA* pulmonary artery, *ICH* intracranial hemorrhage

PE was attributed to a 50-mg dose of intravenous tPA administered for suspected recurrent PE 48 hours after the trial CDT protocol had been completed. The largest meta-analysis of CDT for PE places the rates of major hemorrhage at 4.65% and intracranial hemorrhage at 0.35% [22], below those seen with systemic thrombolysis [12]. Taken together, and though large-scale data are still absent, these prospective studies suggest that CDT may improve hemodynamics more rapidly compared to anticoagulation alone and may have a lower bleeding risk than systemic thrombolysis.

Currently absent in the study of CDT is its impact on short- and long-term clinically relevant outcomes such as mortality, clinical deterioration, recurrent venous thromboembolism, functional capacity, and quality of life. Preliminary data suggest that roughly half of patients who survive acute PE will develop what some refer to as the "post-PE syndrome," a cluster of symptoms, including exercise intolerance and breathlessness and decreased quality of life [23]. Post-PE syndrome and its most severe manifestation, chronic thromboembolic pulmonary hypertension (CTEPH, see Chapter "Epidemiology and Diagnosis of Chronic Thromboembolic Pulmonary Hypertension"), are believed to arise secondary to altered pulmonary perfusion and chronic right ventricular dysfunction. Whereas early systemic thrombolysis may mitigate the risk of developing post-PE syndrome, CDT's contribution is unknown [24, 25]. Given the large unmet need, the role of CDT in improving short- and long-term outcomes after PE has been established as a primary research priority by the Society of Interventional Radiology [5, 26].

Contraindications to Catheter-Directed Therapy

The contraindications to CDT are similar to those of systemic thrombolysis due to the use of a thrombolytic agent. CDT is contraindicated in those with recent ischemic stroke or intracranial hemorrhage (2 months), intracranial mass, vascular malformation, recent neurological (3 months), or abdominopelvic surgery (<10 days), gastrointestinal ulcer, recent active bleeding (<10 days), major internal bleeding in 6 months, or bleeding diathesis. Whether these represent absolute or relative contraindications require Individual risk assessment at the discretion and consensus of the multidisciplinary pulmonary embolism response team. Left bundle branch block is also a contraindication to CDT, as right heart catheterization can induce a right bundle branch block and cause complete heart block—this may require pre-procedure placement of transvenous pacing catheter. History of allergic reaction to iodinated contrast material may require premedication.

Preparation for Catheter-Directed Therapy

First, the interventionalist should review available imaging, including prior CT pulmonary angiography and lower extremity duplex ultrasonography, to determine relevant vascular anatomy, the location, and extent of the target pulmonary emboli, and

assess the presence and extent of deep venous thrombosis, which may influence the choice of access site. A 12-lead ECG should be reviewed to assess the risk of arrhythmia and heart block. Particularly in cases of high-risk PE, an interventionalist may consider recruiting the assistance of cardiac anesthesiology given the complex physiology of the right ventricle. Of note, positive-pressure ventilation reduces preload in an already-strained right heart, and sedative agents can reduce RV preload, which can precipitate a hemodynamic collapse. Finally, the team should be prepared to initiate lifesaving maneuvers (e.g., ECMO, rescue embolectomy in OR) and should make the staffing physician of a medical or surgical ICU aware of a potential admission to their unit postprocedure.

Procedure Walkthrough

Venous Access and Approach Ultrasound-guided anterior wall puncture of the right common femoral vein is the most common means of achieving venous access in CDT for PE, providing a direct course to the right heart via the inferior vena cava. In the event of large thrombus being present in the inferior vena cava and/or iliac/femoral veins, jugular venous or upper extremity venous access (e.g., basilic, brachial, cephalic) may be warranted. After achieving access to the desired vein with a micropuncture needle kit, a 5-F introducer sheath is placed and a pigtail, balloon-tipped, or cobra-shaped catheter is advanced over a guidewire to the right heart. The ECG should still be closely monitored as sustained cardiac arrhythmias can portend worse prognosis in PE [27].

Pressure Measurement and Pulmonary Angiography With a catheter in the right heart, measurement of right atrial, right ventricular, and pulmonary arterial pressures is then performed. Right heart pressures provide baseline hemodynamic information that will be used to monitor the progress of CDT and assess the severity of pulmonary hypertension prior to performing pulmonary angiography. Standard pulmonary angiography protocols call for an injection of 30–40 mL nonionic, low-osmolality contrast at 20–25 mL/s (recorded at 6 frames/s). In the setting of severe pulmonary hypertension, the injection may be decreased to 10–15 mL/s for a volume of 20–30 mL [28]. For reference, normal right atrial pressures are 1–5 mmHg, right ventricular pressures are 15–30 mmHg peak systolic and 1–7 mmHg end-diastolic, and pulmonary arterial pressures are 15–30 mmHg peak systolic and 4–12 mmHg end-diastolic, with mean pressures of 9–19 mmHg [29]. Using preprocedure imaging as a guide, the right and/or left pulmonary artery are (is) selected and a pulmonary angiogram is performed. More selective pulmonary angiograms may be performed at the interventionalists discretion, or not at all if preprocedure imaging is sufficient to guide catheter placement.

Mechanical Catheter-Directed Therapy Mechanical CDT, if performed (e.g., in high-risk PE), is carried out with or without thrombolytic infusion (Fig. 1). Multiple methods of mechanical CDT have been described, the most common being rotating

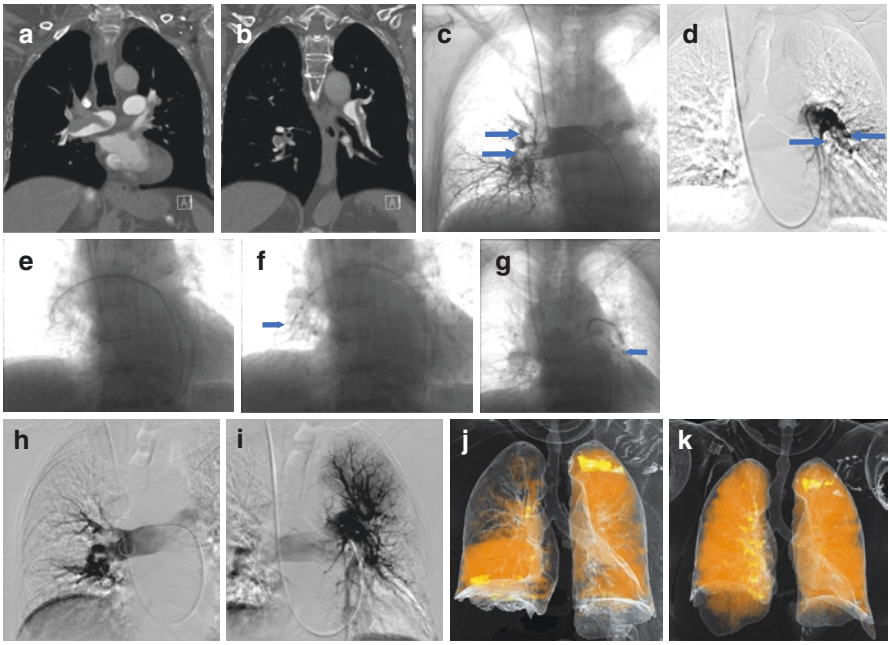

Fig. 1 Images from a 75-year-old woman with a history of remote benign intracranial mass resection who was brought to the emergency department after a fall associated with 3 days of worsening dyspnea; she was found to have an intermediate-risk PE (**a**, **b**) Coronal sections of a CT pulmonary angiogram showing acute pulmonary emboli within the right main (**a**) and left lobar (**b**) pulmonary arteries. (**c**, **d**) Via right internal jugular venous access, diagnostic catheter angiograms of the right (**c**) and left (**d**) pulmonary arteries were performed localizing occlusive thrombus in the right main pulmonary artery and left lower lobe pulmonary artery (arrows). (**e**) An 8-F vascular sheath was positioned in the pulmonary trunk to facilitate catheter-directed thrombolysis. (**f**, **g**) An Indigo CAT8 (Penumbra, Inc.) mechanical thrombectomy catheter was advanced through the vascular sheath and manipulated within the right (**f**) and left (**g**) pulmonary arterial trees to macerate occlusive thrombus (arrows). (**h**, **i**) Repeat catheter angiography of the right (**h**) and left (**i**) pulmonary arterial trees revealed decreased clot burden. (**j**, **k**) Preprocedure (**j**) and postprocedure (**k**) dual-energy CT pulmonary blood volume iodine maps revealing improved perfusion of the right upper lobe and left lower lobe. The patient tolerated the procedure well and was discharged on the sixth postprocedure day on lifelong anticoagulation

pigtail fragmentation, reportedly performed alone or as a component of therapy in 70% of CDT cases worldwide [1, 30]. In rotating pigtail fragmentation, a standard 5-F pigtail catheter is advanced coaxially over a wire and positioned distal to the thrombus, formed into a pigtail, and then spun manually back-and-forth while being retracted proximally through the thrombus. Additional fragmentation via wire disruption or via balloon angioplasty with a balloonsized smaller than the target arterial diameter has also been described [1]. In the event mechanical clot fragmentation causes distal embolization yielding a rise in pulmonary artery pressure, aspiration thrombectomy with an end-hole catheter may be used as an adjunctive method of clot debulking [31]. New devices are rapidly entering the PE market [e.g., Flowtriever

(Inari Medical), Indigo CAT8 (Penumbra, Inc.), Cleaner (Argon Medical)], and may be used on or off-label to restore pulmonary artery flow. Mechanical CDT may be concluded upon resolution of shock with the improvement of the patient's hemodynamics—less credence is given to the angiographic appearance of the pulmonary arteries [32]. If the patient can tolerate additional therapy following mechanical CDT, the interventionalist may proceed with pharmacologic CDT.

Pharmacologic Catheter-Directed Therapy To proceed with pharmacologic CDT, the guidewire used for pulmonary angiography and/or mechanical CDT is exchanged for a medium or stiff wire (e.g., Rosen or Bentson) over which a long vascular sheath is advanced into the main pulmonary artery. Long sheaths provide enhanced stability to the infusion catheters once in place, limiting unwanted motion, or retraction of the catheter during thrombolytic infusion, and permit serial pulmonary artery pressure measurements for monitoring therapy. With the vascular sheath in place, a multisidehole infusion catheter with infusion length of 10–15 cm is advanced over the wire into the pulmonary artery. There, the wire and catheter are advanced in tandem and embedded within the thrombus, at which point a bolus of thrombolytic agent (i.e., 2–6 mg alteplase) may be administered directly into the clot, followed by initiation of thrombolytic infusion. Most infusion protocols call for infusion of 1–2 mg tPA per hour for a total dose of 24 mg. If bilateral catheters are used, an infusion rate of 0.5–1 mg tPA per hour per catheter is recommended.

Upon initiation of thrombolytic infusion, therapeutic anticoagulation is stepped down to subtherapeutic levels and dripped through the vascular sheath for the duration of the infusion (e.g., unfractionated heparin 300–500 U/h, titrated to an activated partial thromboplastin time <60 seconds) for the purposes of reducing perisheath clot formation and minimizing bleeding risk. Along with a complete blood count and routine coagulation labs, fibrinogen levels can be monitored every 4–6 hours for the duration of thrombolytic infusion. If fibrinogen levels fall below 100–150 mg/dL, consideration should be given to reducing or halting thrombolytic infusion and/or transfusing cryoprecipitate or fresh frozen plasma. In the event of major hemorrhage, thrombolytic infusion should be stopped immediately.

During infusion, strict patient-handling orders are implemented and every precaution should be taken to prevent catheter dislodgement [33]. Vascular sheaths and infusion catheters should be sutured in place with Prolene or Nylon sutures and secured with adhesive surgical dressings. With femoral vein catheterization, patients should be kept on bed rest with strict nursing instruction to keep the patient's lower extremities extended at the hip. This minimizes the risk of femoral access site complications and infusion catheter dislodgement. Patients are kept either on NPO or on a clear liquid diet and serial neurologic exams and vascular access site checks are performed every 2 hours to monitor for bleeding complications.

Upon conclusion of the thrombolytic infusion, all endovascular devices and vascular sheaths are removed and manual compression of the vascular access site is performed for 30–45 minutes to achieve hemostasis. Following this, therapeutic anticoagulation may be resumed.

Periprocedural IVC Filter Placement

Following CDT, an interventionalist may choose to conclude therapy by placing an IVC filter. Periprocedural IVC filter placement is controversial. While some studies have shown a mortality benefit with IVC filter placement in high-risk PE, possibly due to reduction of recurrent PE, there is no convincing role for IVC filter placement in patients with intermediate-risk PE who can tolerate therapeutic anticoagulation [34].

Follow-Up Care

Longitudinal follow-up is critical in the proper care of patients with PE. Semiannual evaluation on an outpatient basis ensures adequate anticoagulation and prompt recognition of the long-term sequelae of PE, namely chronic breathlessness and exercise intolerance. For patients who had an IVC filter placed during their hospitalization, outpatient follow-up also improves rates of filter retrieval and therefore mitigates the risks associated with long-term filter implantation [35]. These patients should be scheduled for filter retrieval once filtration is no longer indicated.

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Role of Surgical Embolectomy and ECMO in PE

Dale Shelton Deas Jr. and William Brent Keeling

Abbreviations

AHA	American Heart Association
CPB	Cardiopulmonary bypass
CPC	Cerebral performance category
CPR	Cardiopulmonary resuscitation
CS	Cardiogenic shock without arrest
CS/CA	Cardiogenic shock with cardiac arrest
ECMO	Extracorporeal membrane oxygenation
NCS	No cardiogenic shock
PA	Pulmonary artery
PE	Pulmonary emboli
SPE	Surgical pulmonary embolectomy
SPEAR	Surgical pulmonary embolectomy as routine therapy
STS ACSD	Society of Thoracic Surgery Adult Cardiac Surgery Database
VA	Venoarterial

The History of Surgical Therapy for Acute Pulmonary Emboli

In many ways, surgery for acute pulmonary emboli (PE) mirrors the timeline of the development of cardiac surgery over the past century. Trendelenburg [1] first described surgical embolic extraction over 100 years ago in 1908. The procedure he described was performed, albeit unsuccessfully by him, through a left anterior

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thoracotomy with direct access to the pulmonary artery. Trendelenburg's pupil, Kirschner [2], subsequently performed the first successful surgical pulmonary embolectomy (SPE) in 1924. In the decades that followed, the experience with the Trendelenburg procedure expanded, but the results were not encouraging. Gibbon [3] reported that 9 out of 142 patients survived SPE to hospital discharge. Discouraged by these outcomes, Gibbon perseverated on ways to support the cardiopulmonary circulation during the performance of the Trendelenburg procedure, and it was this perseverance that provided the impetus for the development of the cardiopulmonary bypass (CPB) machine.

Throughout the 1950s and early 1960s, CPB was increasingly utilized to perform a number of open cardiac procedures, and Sharp [4] and Cooley [5] were the first in the early 1960s to perform pulmonary embolectomy utilizing CPB. From that point up until the first part of the twenty-first century, surgical pulmonary embolectomy was largely reserved for patients in extremis or who had suffered prior cardiac arrest as the final attempt at salvage. Not unexpectedly, operative mortality exceeded 30% during this era [6].

In the early 2000s, SPE resurfaced due to the development of CT pulmonary angiography and its superior ability to accurately diagnosis PE and provide meaningful anatomic detail. A report by investigators at Brigham and Women's Hospital showed a 93% survival to discharge for patients who underwent timely diagnosis with CT angiography and early operative intervention. As a result, SPE began to gain wider traction as primary therapy for an expanding cohort of patients in select centers [7, 8].

SPE and Outcomes in the Modern Era

In 2011, the American Heart Association (AHA) issued a scientific statement on PE categorizing patients with specific physiologic criteria as higher risk. Patients with massive PE were either dependent on inotropic agents, had suffered cardiac arrest, or had persistent bradycardia. Patients with submassive PE had evidence of right ventricular dysfunction (defined as an RV/LV ratio $\geq$0.9 on either CT or echocardiography), myocardial necrosis by having a positive serum troponin I, or both [9–11]. Patients with low-risk PE had none of the above criteria.

The new classification system led to re-appraisals of interventional therapy for PE to include surgery. In 2016, Keeling and colleagues [10] reported on one of the first multicenter experiences known as the SPEAR working group (Surgical Pulmonary Embolectomy As Routine therapy) regarding SPE for acute pulmonary emboli. Between 1998 and 2014, four high-volume international institutions performed surgery for 214 patients with acute, life-threatening PE. Each institution accessed data through the local Society of Thoracic Surgeons database, so analysis of granular patient-level data was possible. In-hospital mortality for this series was

11.7%, and this was largely driven by patients with preoperative cardiac arrest who experienced an in-hospital mortality of 32.1%. In utilizing the AHA classification system [10, 11], the SPEAR working group divided their patient population into massive (17.8%) and submassive PE (82.2%). Mortality for the massive PE arm was 23.7%, while the submassive PE arm remained low at 9.1%. In addition, two-thirds of patients undergoing preoperative cardiopulmonary resuscitation (CPR) for acute PE survived SPE. The mortality rate reported in this large series was less than half the mortality rate of the Nationwide Inpatient Sample [10, 12] (27.2%) performed within the same time period between 1999 and 2008 by Kilic and colleagues. The researchers in the SPEAR working group concluded that SPE is in fact remarkably safe when appropriate patient selection is utilized at high volume centers.

In 2018, Kon and colleagues [13] published the results of their study looking at all surgery for PE as reported in the Society of Thoracic Surgery Adult Cardiac Surgery Database (STS ACSD). In their report, patients ($n = 1075$) were categorized into one of three cohorts: no cardiogenic shock (NCS; $n = 719$), cardiogenic shock without arrest (CS; $n = 203$), and cardiogenic shock with cardiac arrest (CS/CA; $n = 153$). Of the 1144 hospitals reporting to the STS ACSD, 310 centers in North America performed at least one SPE, averaging 0.91 ± 1.4 cases/year per hospital (Fig. 1). Of note, only seven centers in North America averaged >5 SPEs per year. Patients in CS were significantly more likely to present with syncope, unresponsive neurologic status, require preoperative inotropes or IABP, and receive preoperative thrombolysis. Emergent salvage operations were more common in patients in CS

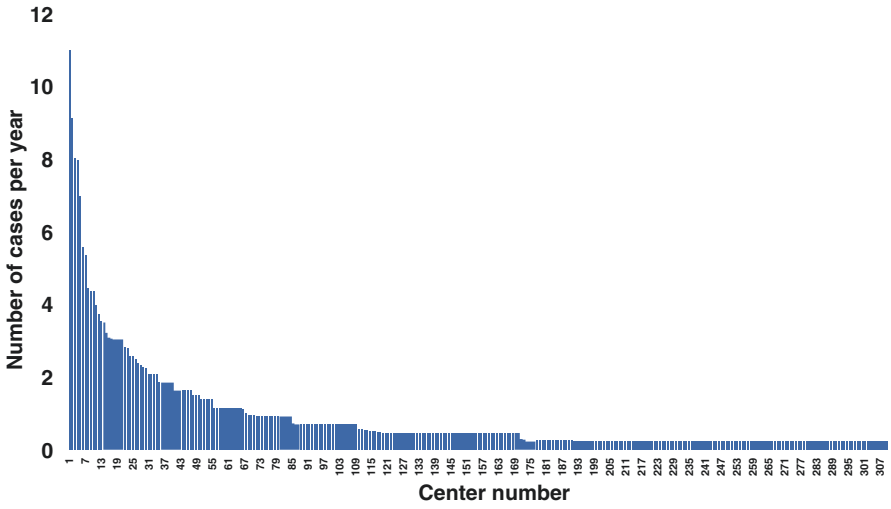

Fig. 1 Number of SPE cases per year per hospital performed in North America

needing CPR. Of note, beating heart techniques were more likely to be used in CS patients needing CPR compared to CS without CPR and NCS groups. There was no difference in major morbidity within CS patients irrespective of utilizing CPR. Operative mortality within the STS ACSD study comprising all 310 centers in North America was 16% (NCS = 8%, CS = 24%, CS/CA = 44%) compared to the four centers in the SPEAR working group with an operative mortality of 11.7%. Multivariate analysis showed that the strongest predictor of operative mortality was CS +/− CPR, moderate to severe chronic lung disease, and unresponsive neurologic state. Interestingly, preoperative inotropes or IABP, ECMO, and thrombolysis were not associated with operative mortality.

The study of Kon and colleagues [13] demonstrated what most providers already suspected – that surgery for PE is rarely performed. The STS ACSD study supports the referral of patients with massive or submassive PE to high-volume institutions. In fact, Kon and colleagues [13] pointed out that single-center series have achieved short and mid-term mortality rates following SPE as low as 0–3% in submassive PE patients and 3–35% in CS patients +/− CPR [10, 13–15]. Interestingly, the study based on the National Inpatient Sample [12, 13] prior to Kon's work showed a higher number of annual cases per hospital (2.3) compared to 0.91 ± 1.4 cases/year per hospital nearly a decade later. This illustrates that more hospitals are beginning to adopt SPE as a modality for the treatment of acute PE (an increasing institution number despite a lower mean per hospital) compared to years past, with mortality rates declining.

There is little published data regarding the mid- to long-term outcomes following SPE. In a 2016 publication, surgeons [16] at Emory University reported mid-term echocardiographic follow-up results following SPE. Patients who underwent SPE showed immediate and durable improvement in right ventricular hemodynamics at a median follow-up of almost 3 years (Table 1). There is a growing body of evidence that SPE should be considered as a first-line option in the treatment of massive and submassive PE.

Table 1 A comparison of preoperative echocardiographic data with a median follow-up

	Preoperative value ($n = 21$)	Follow-up ($n = 12$)	P-value
Moderate or greater ventricular dysfunction	17 (81.0%)	1 (8.3%)	<.0001
Moderate or greater tricuspid regurgitation	6 (28.6%)	0 (0)	.0005
Pulmonary artery systolic pressure (mm Hg)	51.2 ± 21.6 ($n = 17$)	37.2 ± 14.2 ($n = 9$)	.01
Tricuspid valve regurgitant velocity (m/s)	3.1 ± 0.8 ($n = 16$)	2.4 ± 0.7 ($n = 11$)	.03

SPE provided significant improvement in right ventricular hemodynamics, including right ventricular function, decreased tricuspid regurgitation, and lowering of pulmonary artery pressures over a median time-interval of almost 3 years

Indications for Surgical Pulmonary Embolectomy

Despite advances in surgical technique, patient selection, mechanical circulatory support, and postoperative care, the overall utilization of SPE for acute, life-threatening PEs remains low. Lee and colleagues [17] recently cited an SPE rate of 0.14% (thrombolysis 1%) in the setting of acute PE (based on ICD-9 code for PE-415.1x) using a robust statewide database. These data are comparable to reports from the Nationwide Inpatient Sample [18, 19] on rates of surgery for the treatment of acute PE. Nonetheless, enhanced awareness of the use of SPE in the setting of massive and centrally located PE is growing, though briefly mentioned, as evidenced by its inclusion in the treatment guidelines for acute PE from the American Heart Association, American College of Chest Physicians, and the European Society of Cardiology in recent years [9, 20, 21].

Surgery is likely the preferred treatment modality for certain patients including those with a high risk of bleeding, a history of intracranial hemorrhage, recent ischemic stroke, age greater than 75, or major surgery in the past month. SPE can also be utilized for other, high-risk scenarios including failure of thrombolysis (but with a very high risk of perioperative hemorrhage) or thrombus-in-transit [22–24].

Surgical Procedure

Given the significant risk of cardiac arrest imposed by the induction of anesthesia, patients are first prepped and draped prior to intubation. Certain high-risk patients including those on inotropic therapy will have percutaneous femoral access placed prior to induction. General anesthesia is then induced. Most procedures are performed through a median sternotomy with central aortic cannulation. Alternative access to the main pulmonary artery can be obtained through a left anterior thoracotomy. Venous cannulation is usually via the right atrium, but bicaval venous cannulation can be performed for thrombus-in-transit or when there is a sizable patent foramen ovale that must be repaired. Systemic heparin is administered, and normothermic cardiopulmonary bypass is then initiated. Cardioplegic arrest is only necessary when concomitant intracardiac procedures are performed necessitating access to the cardiac chambers.

A 4-0 monofilament suture is placed just cephalad to the pulmonary valve and retracted caudally. This retraction stitch provides terrific exposure to the entirety of the main pulmonary artery. The aorta is fully mobilized and encircled with a snare. The main pulmonary artery (PA) is then sharply incised in a longitudinal fashion beginning two centimeters cephalad to the pulmonary valve and extending almost to the bifurcation of the main PA. This technique provides excellent exposure to the left PA system. Aortic root retractors are inserted into the pulmonary arteriotomy in order to facilitate exposures down to the sublobar level bilaterally. Additionally, the operating surgeon switches sides of the table in order to better visualize the

respective distal branches. A variety of methods are then utilized to remove embolic material including surgical forceps, gentle suction, and thoracoscopic instruments. Occasionally, the thoracoscope is utilized in order to directly view the sublobar branches of each PA system. A counterincision is not routinely made in the right main pulmonary artery in between the superior vena cava and the aorta, but this incision is made in a minority of procedures where exposure is difficult.

Following the completion of pulmonary embolectomy and irrigation, pulmonary arteriotomies can be closed in layers using a 5-0 monofilament suture. Once the arteriotomies are closed, cardiopulmonary bypass is weaned. With the assistance of inotropy and inhaled epoprostenol, separation from cardiopulmonary bypass without any further mechanical support is typically achieved. Right ventricular function is monitored closely throughout this process both visually and via transesophageal echocardiography. Decannulation is then performed and systemic protamine is administered.

Once hemostasis has been achieved, the thorax is closed. Key elements of perioperative management include pharmacologic support of the right ventricle, early initiation of systemic anticoagulation at 6 hours after the operation, and added mechanical circulatory support when needed.

SPE as First-Line Therapy

In 2013, Aymard and colleagues [25] proposed SPE to be the first-line treatment for patients with life-threatening PE. They analyzed 80 patients with massive PE who underwent either systemic thrombolytic therapy, surgical embolectomy, or surgery after failure of thrombolysis. SPE was associated with a statistically similar early mortality when compared to thrombolysis (3.6% vs. 13.5%) and had significantly fewer bleeding complications (3.6% vs. 26.5%). Importantly, they showed that patients who underwent surgery after failed thrombolysis had worse outcomes (mortality of 27%), suggesting there may be scenarios where SPE should be pursued as a first-line approach [22, 25].

In a separate study, Lee and colleagues [17] reported no difference in 30-day (15.2% vs. 13.2%) or 5-year mortality (72.4% vs. 76.1%) between thrombolysis (n = 1854; 88%) or SPE (n = 257; 12%). Interestingly, thrombolysis was found to be associated with a higher risk of stroke (1.9% vs. 0.8%) and reintervention (3.8% vs. 1.2%) at 30 days, and was associated with a higher likelihood of recurrent PE requiring subsequent inpatient readmission (7.9% vs. 2.8%). While they stopped short of recommending that SPE be the first-line therapy for patients with life-threatening PE, they did propose the development of algorithms for SPE when thrombolysis was contraindicated.

The results reported by Aymard [25] and Lee [17] help to support SPE as the initial therapy given comparable survival rates to thrombolytics. Moreover, SPE following failed thrombolysis is associated with poor outcomes and decreased short-term survival, thus reinforcing the need to include SPE in the armamentarium of first-line therapies for life-threatening PE.

VA-ECMO in PE

Extracorporeal membrane oxygenation (ECMO) is increasingly being used in the setting of SPE, but its exact role remains as of yet unclear. Venoarterial (VA)-ECMO serves to decrease RV overload and afterload, improves RV function, and summarily improves oxygen delivery to peripheral tissues [26]. Historically, VA-ECMO was used as a salvage mechanism after failing conventional pharmacologic and mechanical support measures. In recent years, VA-ECMO has taken on a larger role within the treatment algorithm of life-threatening PE and is increasingly being utilized as up-front support prior to or at the onset of SPE.

Yusuff and colleagues [27] performed a systematic review of patients who were supported by VA-ECMO in the setting of large, life-threatening PEs. Nineteen studies containing 78 patients were included, and the survival to discharge was 70.1%. Survival was not significantly different when VA-ECMO was used in conjunction with systemic thrombolysis, catheter-based embolectomy, or SPE. Cardiac arrest did increase mortality in this cohort of patients, but it is unclear what role ECMO played as a salvage technique in this aggregated study. In 2015, Schmidt and colleagues [28] constructed a survival-prediction model that showed a lower predicted chance of survival for each additional extracardiac organ to fail when initiating VA-ECMO. Early initiation of VA-ECMO is becoming increasingly important in the setting of massive PE. In 2018, Pasrija and colleagues [29] reported on their series of 20 patients who underwent ECMO who also suffered massive PE. All patients had RV/LV ventricular ratio >1, severe RV dysfunction, and signs of end-organ dysfunction. If thrombus burden resolved after the initiation of VA-ECMO, the patient was decannulated (40%, anticoagulation alone). If significant clot burden persisted with indications of RV strain, an operative intervention was pursued (55% SPE, 5% catheter-directed therapy). There was a 100% survival ($n = 11$) for patients undergoing VA-ECMO with subsequent SPE. Pasrija and colleagues [29] believed after reviewing their results that establishing VA-ECMO early limits ischemia by establishing perfusion, mitigates permanent end-organ damage, and prevents cardiac arrest. Their study supported the use of awake VA-ECMO in all nonintubated patients because intubation and wire manipulation in the RV can precipitate cardiac arrest. VA-ECMO first offers early restoration of perfusion, reflected in the study outcomes whereby all patients had a cerebral performance category (CPC) score of 1 (good cerebral performance). RV function also dramatically improved because of RV decompression, and no patients were discharged from the hospital with subsequent RV dysfunction.

In 2018, researchers [11] at the University of Maryland discussed their improved protocol (Fig. 2). All patients enrolled in the study had elevated troponin levels, severe RV dysfunction, and an RV/LV ratio >1. In the historical arm, SPE was performed on all patients (100%, $n = 27$), but only 48% of patients ($n = 14$) underwent SPE within the new protocol. All patients with end-organ dysfunction or unclear neurologic status underwent VA-ECMO in the protocol group. There was a significant difference between the number of patients placed on VA-ECMO first between

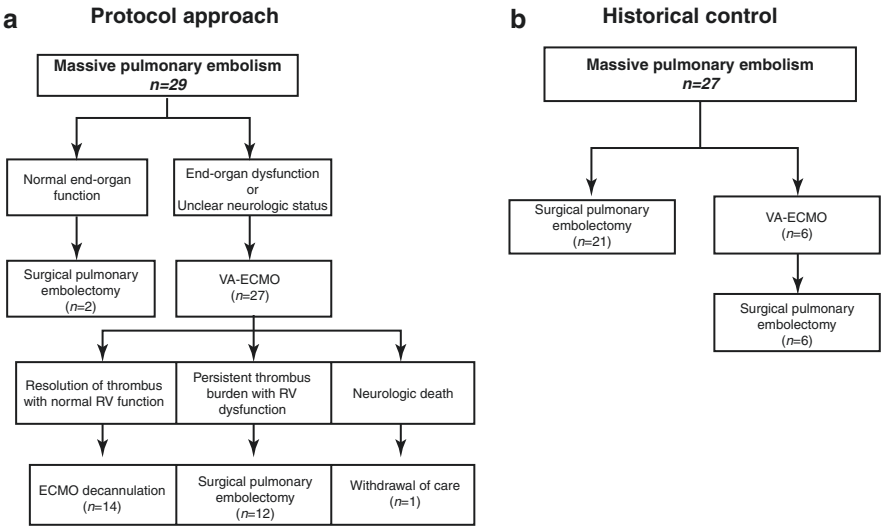

Fig. 2 Therapeutic strategy for patients in the protocol approach group (**a**) and historical group (**b**). From the University of Maryland, patients in the protocolized group achieved a 0% intraoperative arrest rate following induction of anesthesia and a 100% in-hospital survival rate compared to 15% and 82%, respectively, in the historical group of 100% SPE patients. Protocolizing patients with end-organ dysfunction and unclear neurologic status to VA-ECMO first allowed for enhanced recovery of end-organ dysfunction, RV function, and overall survival with or without SPE. VA-ECMO Veno-arterial extracorporeal membrane oxygenation, RV right ventricular, ECMO extracorporeal membrane oxygenation

the historical and protocol group (22% vs. 93%, $p < 0.001$). Patients within the protocol group undergoing VA-ECMO as the primary intervention were on ECMO for a median of 5.8 days compared to 1.0 day for the historical group where primary intervention was SPE ($p < 0.001$). They believed that the extended time on VA-ECMO in the protocol group allowed for enhanced recovery of end-organ dysfunction as well as RV function. Within the historical group, induction of anesthesia resulted in an intraoperative arrest rate of 15% compared to 0% in the protocol group ($p = 0.05$). Interestingly, all patients survived in-hospital within the new protocol undergoing SPE versus 82% for the historical group. At 1-year, estimated survival was significantly lower for the historical group compared to the protocol group on Kaplan–Meier analysis (73% vs. 96%, $p = 0.02$) (Fig. 3). On Cox regression analysis, the historical group was determined to be a predictor for mortality (HR 8.350; CI 1.027–67.894; $p = 0.01$). Of note, unclear neurologic status was present in 4 of 5 in-hospital mortalities in the historical group where the patients were deemed to be in extremis and sent rapidly to the operating room. Initiation of VA-ECMO first established early return of perfusion and the ability to determine neurologic status, which was determined for all patients within the protocol group in the first 48 hours. This reflects an improved awareness of appropriate operative selection afforded by early hemodynamic support with VA-ECMO.

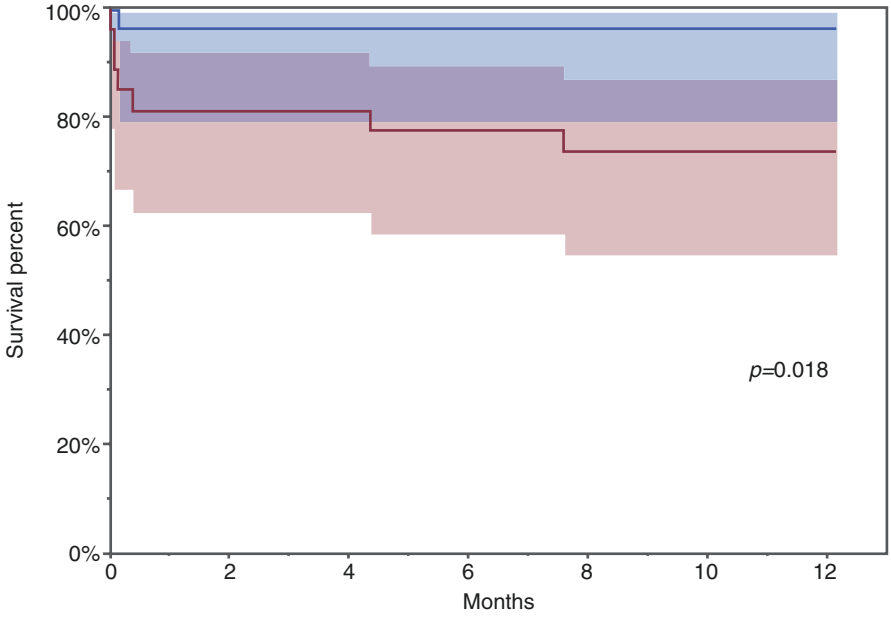

Fig. 3 Kaplan–Meier survival curves for patients in the protocol approach group (blue) and the historical control group (red). At 1-year, estimated survival was significantly lower for the historical group compared to the protocol group, 73% vs. 96% respectively, $p = 0.02$. (Report from the University of Maryland)

Conclusion

SPE is increasingly becoming utilized in select patients for the management of life-threatening acute submassive and massive PE. In the report herein, numerous studies have shown promising results of a "surgery first" and initial, though judicious, use of upfront VA-ECMO to optimize the patient prior to SPE. Though major referral centers for SPE are limited, outcomes at smaller volume and rural hospitals have proven excellent and can be lifesaving. The addition of randomized control trials would help distinguish the nuances of patient selection and the type of therapy employed.

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Inferior Vena Cava Filters in Venous Thromboembolism

Robert M. Marron, Parth Rali, and Todd M. Bull

Introduction and Background

Venous thromboembolic disease (VTE) is the third most common cause of cardiovascular disease, following only myocardial infarction and stroke [1]. Over one million cases of pulmonary embolism (PE), the most life-threatening form of VTE, occur annually in the United States and Europe combined [2, 3]. Interventions that help decrease the morbidity and mortality of this disease are of great interest and importance. While the primary treatment for VTE is anticoagulation, placement of a mechanical barrier within the inferior vena cava (IVC) has been considered a secondary treatment approach for many years. This chapter will review the available data regarding the use and complications of IVC filters as a secondary treatment option for VTE.

The concept of interrupting the inferior vena cava (IVC) in hopes of preventing the migration of venous thromboembolic disease to the pulmonary vasculature is not novel. Prior to the advent of implantable IVC filters, alternative methods to prevent embolization of deep venous thrombosis (DVT) to the pulmonary arteries included femoral vein or IVC plication or ligation, described initially in 1934 [4, 5]. While practically these options prevented migration of DVT, they led to high complication rates. One group reported a mortality rate of 12% in patients receiving surgical ligation or plication of the IVC without cardiac disease and 41% in patients with severe cardiac disease [5, 6]. Another analysis determined higher-risk cardiac patients had a mortality rate as high as 60% [7]. While reportedly effective in

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preventing PE, the potential for complications and the long-term morbidity and mortality of such an approach made these surgical options untenable in most situations. In 1967, the Mobin-Uddin umbrella filter was introduced as an extraneous means of preventing migration of DVTs to the pulmonary vasculature. In 1972, Dr. Mobin-Uddin's group reported a case series of 100 patients in the *New England Journal of Medicine* that determined IVC filter placement was a safer option than surgical ligation of the IVC and was effective in preventing pulmonary embolism [5].

Numerous filter designs have been adopted since – including the advent of retrievable and convertible IVC filters. Several more are currently under development. The utility of these devices and their appropriate application is an area of debate. There have been only two randomized controlled trials investigating the efficacy of IVC filters in the setting of VTE, and in both of these studies, the patients received full anticoagulation. The potential for adverse outcomes associated with IVC filter use is well recognized.

Types of IVC Filters

Two general types of IVC filters – permanent and retrievable filters – are widely available for use, while a third type – a convertible IVC filter – has recently been approved by the FDA. Permanent IVC filters have been available since the late 1960s and are typically placed in patients with long-term or permanent absolute contraindications to anticoagulation with a long-term need to mechanically prevent PE [8, 9]. Optional (or retrievable) IVC filters were developed in the 1990s and can be removed if contraindications to anticoagulation or risk of PE resolve. All filters are designed to maximize the ability to trap clots that are in transit while allowing optimal venous blood flow to the heart. The advent of retrievable IVC filters led to an expansion of indications for filters. This along with the development of multiple filter designs led to an increase in filter placement [10]. No data exists that suggests any one type of filter is more effective than others; however, the US Food and Drug Administration (FDA) issued a warning in 2010 that was updated in 2014 stating that healthcare providers should remove retrievable IVC filters once they are no longer needed [11].

Indications for Filter Placement

The classic indication for placement of an IVC filter is the presence of a VTE with an absolute contraindication to anticoagulation [12, 13]. Expanded indications include scenarios where IVC filters are used as an adjunct to anticoagulation, such as recurrent VTE, progression of a DVT, massive or high-risk PE with concurrent DVT and increased risk of death from secondary embolization, iliocaval or

free-floating proximal DVT, thrombolysis of iliocaval DVT, massive PE treated with thrombectomy or thrombolysis, difficulty maintaining therapeutic anticoagulation, and high-risk for complication of anticoagulation [13–15]. Prophylactic indications for IVC filter placement are those in which a VTE has not occurred but a patient is at high risk of developing DVT with or without PE. Prophylactic retrievable IVC filters are placed primarily in trauma patients at high risk of VTE who cannot receive prophylactic anticoagulation and patients undergoing surgical procedures with an inherent elevated risk of VTE such as bariatric surgery [13, 16]. Despite limited data from research studies, the prevalence of prophylactic use of IVC filters has increased since the advent of retrievable devices [13, 17]. A randomized controlled trial published in 2019 examined the use of prophylactic IVC filters in trauma patients. The placement of IVC filters did not significantly decrease mortality or symptomatic PE [18]. Several large registry studies have suggested that IVC filter placement can reduce early mortality in patients with acute VTE, but the inherent weaknesses of such studies have led to a lack of consensus about the strength of this evidence [18–23].

All professional societies concur that temporary IVC filters are indicated in patients that present with VTE who have an absolute contraindication to anticoagulation [12, 14, 15, 25, 26]. This agreement comes without a randomized clinical trial to validate that filters improve mortality. It is unlikely that such a trial will be undertaken, as it may be difficult for clinicians to withhold IVC filter use in a randomized trial in patients with VTE and an absolute contraindication to anticoagulation given the recommendations that they be used. In 2018, a comparative effectiveness, retrospective cohort study used a population-based sample of hospitalized patients with VTE and a contraindication to anticoagulation using large databases with patient information and outcomes. After adjusting for immortal time bias to eliminate overstated benefits in the intervention arm, it found an associated increase in 30-day mortality in patients receiving IVC filters [27]. The study was limited as it was retrospective and identified patients by billing codes, could not control for confounders, and included relative contraindications rather than solely absolute contraindications. The selection of 30-day mortality as the primary outcome in this group may have also missed a benefit seen in the shorter term, as patients who die from VTE in the hospital often die earlier in the disease course, with 30% of mortality occurring in the first 24 hours [28].

The American College of Chest Physicians (ACCP) discourages the use of IVC filters in anticoagulated patients and opposes their use as prophylaxis against PE [12]. The American Heart Association (AHA) states it is reasonable to place an IVC filter in patients with recurrent PE and/or DVT despite anticoagulation, but they should not be routinely placed in the treatment of ileofemoral DVT or in patients with massive PE treated with thrombolysis or thrombectomy [25]. In 2016, a small cohort study using propensity matching determined that among patients with VTE recurrence despite anticoagulation, IVC filter placement was associated with reduced all-cause mortality at 3 months in patients with recurrent PE, but not in those with recurrent DVT, and PE-related mortality was unchanged [29]. The American College of Radiology (ACR) and the Society for Interventional Radiology

(SIR) have recommend broader indications for IVC filters including placement in patients with recurrent PE despite adequate anticoagulation, an inability to achieve or maintain adequate anticoagulation, propagation, or progression of a DVT during anticoagulation, massive PE with residual DVT in a patient at risk for further PE, free-floating ileofemoral or IVC thrombus, severe cardiopulmonary disease and DVT, as well as prophylactic placement in certain high-risk trauma patients [13–15]. The Eastern Association for the Surgery of Trauma supports consideration of IVC filter placement in very high-risk trauma patients with a contraindication to VTE prophylaxis or anticoagulation and injury patterns that lead to prolonged immobility [13, 16, 30].

Evidence-Based Literature Review

Only two prospective randomized controlled trials (RCT) evaluating the efficacy of IVC filters in patients with VTE have been reported. The first trial was published in 1998, entitled Prevention du Risque d'Embolie Pulmonaire par Interruption Cave (PREPIC) [31]. The PREPIC study was a prospective multicenter, nonblinded RCT that enrolled 400 patients with a proximal DVT (with or without PE) that were deemed to be of high risk for further pulmonary embolism. The study initially intended to recruit 800 patients; however, enrollment was stopped early due to slow recruitment. All patients were anticoagulated initially with heparin and then with warfarin. They were randomized into two groups – one receiving a permanent IVC filter in addition to anticoagulation and the other receiving anticoagulation alone.

Patients at baseline underwent ventilation-perfusion (V/Q) scanning, with a strong recommendation that they receive invasive pulmonary angiography. Imaging was then repeated at 12 days and whenever a suspicion for a new pulmonary embolism arose. The primary end-point was incidence of pulmonary embolism at day 12. The study showed that patients who underwent placement of an IVC filter as an add on therapy to anticoagulation had a significantly reduced risk of PE at 12 days; however, this was offset by an increased risk of recurrent DVT, as well as a lack of reduction in symptomatic PE over the 2-year follow-up period and a lack of an effect on all-cause mortality. The PREPIC authors determined that given the excess of recurrent DVT and lack of mortality benefit, systemic utilization of IVC filters could not be recommended [31].

Eight years later, the PREPIC group reported a follow-up on the patients from their initial study [32]. Patients were called annually to determine if they had symptoms of PE and were encouraged to pursue testing if symptoms were present. The follow-up study reported a decrease in nonfatal PE occurrence, with an increase in DVT occurrence, and no effect on mortality. Concomitant treatment with long-term anticoagulation was similar in both the IVC filter treatment and control groups, suggesting that the increased DVT occurrence in the IVC filter treatment group was not due to differences in rates of anticoagulation [32].

A second randomized controlled trial of 399 patients, known as PREPIC2, was performed after the advent of retrievable IVC filters [33]. All patients were hospitalized with acute, symptomatic pulmonary embolism, as well as DVT, and had at least one marker for severity. These markers included an age over 75, active cancer, chronic cardiac or respiratory insufficiency, recent ischemic stroke with leg paralysis, DVT involving the iliocaval segment or occurring bilaterally, right ventricular dilation, elevated brain natriuretic peptide (BNP), or elevated cardiac troponin. The patients were all anticoagulated for at least 6 months and were divided into a treatment group receiving a retrievable IVC filter and a control group only receiving anticoagulation. All IVC filters were placed with the intention to have them removed after 3 months. At 3 months and at 6 months there were no significant differences between the groups, with a trend toward recurrent PE and increased mortality in the treatment group who received an IVC filter. Filter removal was attempted in 164 of the 193 patients who received a device and was successfully removed in 153 patients [33]. This trial certainly did not add merit to adding IVC filter placement in higher-risk patients with PE and DVT receiving anticoagulation; however, the threshold criteria used to deem a patient high-risk was low and does not match with current practice in risk stratifying PE [34].

While large prospective trials have yielded limited results encouraging IVC filter use, smaller studies have sought to determine if a more selective patient group would benefit from filter placement. A prospective cohort study of patients with VTE and a significant bleeding risk found the group that received an IVC filter had a lower risk of PE-related death, albeit with a higher risk of recurrent VTE, when compared to a propensity-matched control group [35]. Several studies have looked for benefits of IVC filter use in different sub-groups of patients when utilizing a national database and searching for relevant coding. Survival benefits have been found in patients receiving IVC filters with PE who are deemed unstable due to mechanical ventilation or shock, in patients who receive pulmonary embolectomy or who receive thrombolytic therapy, and in patients in whom the IVC filter is placed quickly, or in those who have heart failure or are over the age of 80 [19–21, 23, 24]. A similar retrospective database study found benefit in IVC filter placement in patients with recurrent PE [22]. These studies are retrospective and utilize large national databases and come with inherent limitations. It is unlikely, however, that large randomized controlled trials will be undertaken in these clinical scenarios.

Prophylactic IVC filters do not prevent DVT but are placed in patients at elevated risk of VTE, especially when prophylactic anticoagulation is contraindicated, in the hope that it will prevent symptomatic or fatal pulmonary embolism [13, 18, 36]. The ACCP guidelines recommend against prophylactic use of IVC filters [12]; however, a large single-center retrospective review revealed that approximately half of the IVC filters placed over 8 years were placed prophylactically, with low retrieval rates [36]. Prophylactic IVC filters are typically placed in patients with significant trauma and prolonged immobility with a contraindication to anticoagulation or VTE prophylaxis [18, 36]. They can also be placed prophylactically prior to surgery in certain scenarios – typically prior to bariatric surgery [13, 37].

Trauma patients are at high risk for VTE, given the immobility, endothelial injury, and hypercoaguability – a combination of factors known as Virchow's triad. VTE occurs in up to half of trauma patients who do not receive pharmacologic prophylaxis [38]. In 2002, the Eastern Association of Trauma (EAST) issued guidelines including a recommendation that IVC filters be considered for high-risk trauma patients with long-term anticipated immobility who cannot receive anticoagulation prophylactically [30]. Some retrospective studies have suggested that prophylactic IVC filters may reduce rates of symptomatic and fatal PE in selected trauma patients [39, 40]. Other studies have failed to demonstrate benefit and/or have reported an increased incidence of DVT [41, 42]. Practice varies widely between institutions, with incidence of filter placement in trauma patients reported between 0.6% and 9.6% [41].

In 2019, a multicenter, randomized, controlled trial was conducted in trauma patients with a contraindication to prophylactic anticoagulation and showed no mortality benefit or reduction in symptomatic PE in a group receiving a prophylactic IVC filter compared to a control non-filter group. The treatment group had an IVC filter inserted within 72 hours of presentation. Interestingly, patients who survived at least 7 days but were unable to initiate prophylactic anticoagulation by day 7 had a 14.7% incidence of PE in the control group, while nobody in the treatment had a PE and six were found to have an entrapped thrombus in their IVC filter. This study suggests that not all trauma patients with an initial contraindication to pharmacologic VTE prophylaxis should receive prophylactic IVC filters, but that there may be a select subset of trauma patients who cannot be anticoagulated for an extended period of time, who may benefit from prophylactic IVC filter placement [18].

The rate of VTE in patients undergoing bariatric surgery has been estimated to be as high as 2% even with the use of pneumatic compression devices and perioperative pharmacologic prophylaxis [43]. Dosing of anticoagulation both prophylactically and therapeutically can be difficult in patients with very high body-mass indexes (BMI). Prophylactic IVC filter placement in patients with a BMI >55 has been shown to reduce the risk of PE; however, conflicting evidence exists [44]. A 2015 meta-analysis of 18 studies did not reveal a clear benefit in IVC filter placement; however, a small segment of patients with multiple risk factors for VTE had reduced PE-related mortality [45]. It may be unlikely that a randomized clinical trial will be performed in this population.

Complications of IVC Filters

There are 23 IVC filter types currently in use in the United States [46]. Temporary IVC filters should be retrieved as soon as risk of pulmonary embolism subsides. It is recommended that temporary IVC filters be removed within 29–54 days of placement [11, 47]. Most IVC filters are placed in the hospital setting. Filters are less

likely to be retrieved if patients are not followed up closely after discharge from the hospital, or if their outpatient physicians or healthcare providers are not aware of indications for filter removal. Only one-third of IVC filters is retrieved [17].

Unretrieved IVC filters can lead to a variety of complications such as filter-related thrombosis, deep vein thrombosis, filter migration or embolization, filter fracture, and IVC perforation [17, 46, 48]. Definitions for certain complications are as follows:

A. Filter migration or embolization is defined as >2 cm change in position of a filter compared to its original location.
B. Filter fracture is defined as the structural failure or separation of components of the IVC filter.
C. IVC perforation is defined as the visualization of a filter element >3 mm beyond the lumen of the IVC or within an adjacent structure.

An increased risk of DVT and a reduced risk of PE in patients receiving IVC filters have been reported [32, 49–51]. Risk of DVT varies with IVC filter type (i.e., ALN filter 15.2%, Option filter 18%) and the duration of time the filter remains in place. The longer the filter is in place, the higher the chance of DVT occurrence [32]. It is difficult to fully determine if the IVC filter device itself or underlying host disease contributes to the development of DVTs in these settings, as patients are frequently not being anticoagulated. If underlying host disease is causing DVTs to occur, the IVC filters that are in place may be preventing migration of thrombus and PE.

The overall rate of filter migration is <1% for all filters except the G2 filter that has a migration rate of up to 4.5% (Bard peripheral vascular, Temple, Arizona) [16]. A majority (>90%) of migration events occur in patients with an IVC filter that remains in place for longer than 30 days. The G2 filter also has highest rate of filter fracture (31%) [17, 48]. IVC thrombosis or stenosis has an incidence of 2.8%. Non-fatal IVC perforation rate is around 20%. The retrieval rate of IVC filters remains poor in the United States. When filter retrieval is attempted, however, nearly 95% of filters can be retrieved successfully without complications [17, 48].

The FDA warning regarding IVC filter placement and retrieval in 2010 has led to an overall decrease in the use of IVC filters [11, 52] but has unfortunately not resulted in an increase in filter retrieval rates. Several major IVC filter manufacturers are participating in the ongoing PRESERVE trial (Predicting the safety and effectiveness of Inferior Vena Cava filters, NCT02381509) or conducting studies under the FDA's 522 post-market surveillance program to better understand the long-term complications of IVC filters. We would like to inform the readers that most of the filter complication rates mentioned above are through FDA voluntary self-reporting databases and complication rates therefore may be underreported. Complications may vary significantly among the different filter types, so readers should be aware of local practice to better understand the risk profiles associated with individual filter types.

Future Directions

While the efficacy of IVC filters in reducing incidence of PE has been demonstrated in some (but not all) trials in the acute hospital setting, this benefit must be weighed against the risks of low filter-retrieval rates and potential long-term complications of unretrieved IVC filters. In real-world practice, there exists a group of patients with high-risk sub-massive PE with large, proximal DVTs, who are at risk of cardiopulmonary compromise, as well as patients with VTE who have only a transient indication to stop anticoagulation (i.e., for surgical interventions and temporary bleeding). These patients may benefit from IVC filter placement if potential long-term complications can be avoided. Recently, the development and implementation of multidisciplinary pulmonary embolism response teams (PERT) has created groups of healthcare providers that not only follow patients acutely in the hospital setting but also at short-interval outpatient follow-up visits [53]. PERT teams can potentially reduce the use of unnecessary IVC filters, and patients who receive an IVC filter as a treatment option in this multidisciplinary setting can be followed by PERT providers as an outpatient, and filters may be removed more frequently and expediently.

New technologies are being developed that may also change practice. A type of IVC filter known as the Angel Catheter (Bio2 Medical) is a triple-lumen central venous catheter with a deployable IVC filter at the distal tip that has recently been approved by the FDA. It can be placed at the bedside via the femoral vein in critically ill patients. The device must be removed before hospital discharge, thus avoiding the long-term complications of IVC filters while providing protection in critically ill patients [54].

There is growing interest in the potential role of convertible and bioconvertible IVC filters that do not need to be removed. Convertible devices are placed and serve as filters that can be converted after the need for mechanical prophylaxis of PE passes to an open configuration that no longer filters the IVC. An investigational device exemption multicenter trial was performed with a convertible IVC filter (VenaTech Convertible Vena Cava Filter). This filter was placed in 149 patients, and after a time interval, the patient was assessed for conversion. If deemed appropriate, the device was converted during an interventional radiology procedure where a filter hook was snared and unlocked opening up the filter. The study reported a high rate of filter conversion and a low incidence of adverse effects [55]. Bioconvertible IVC filters do not have to be retrieved and convert on their own without a separate procedure and can offer protection immediately in the setting of VTE [56].

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Multidisciplinary PE Response Team Development and Implementation

Alexandra K. Wong and Richard N. Channick

Background

Up to 100,000 people die in the United States each year as a result of their venous thromboembolic disease, and about 33% of those who survive will have a recurrent event within 10 years [1]. In addition, hospital admissions for pulmonary embolism have increased in recent years [2] (Fig. 1). Over a similar timeframe, there have been significant advances in the approach to the management of this complex and heterogeneous group of patients. Updates in data surrounding initial and long-term anticoagulant choice, systemic or catheter-directed use of thrombolytics for acute pulmonary embolism, as well as surgical and percutaneous techniques for specific cases has resulted in a complex landscape of treatment strategies [3]. Thus, the management of pulmonary embolism has similarly expanded to include providers from a broad range of medical and surgical specialties, including emergency medicine, hematology, pulmonary/critical care, cardiology, vascular medicine, cardiothoracic surgery, radiology, and more. Furthermore, patients presenting with high-intermediate or high-risk pulmonary embolism have high rates of early mortality, requiring efficient mobilization of a multidisciplinary team for rapid decision-making and swift implementation of treatment [4]. In this demanding environment, the pulmonary embolism response team (PERT) was created.

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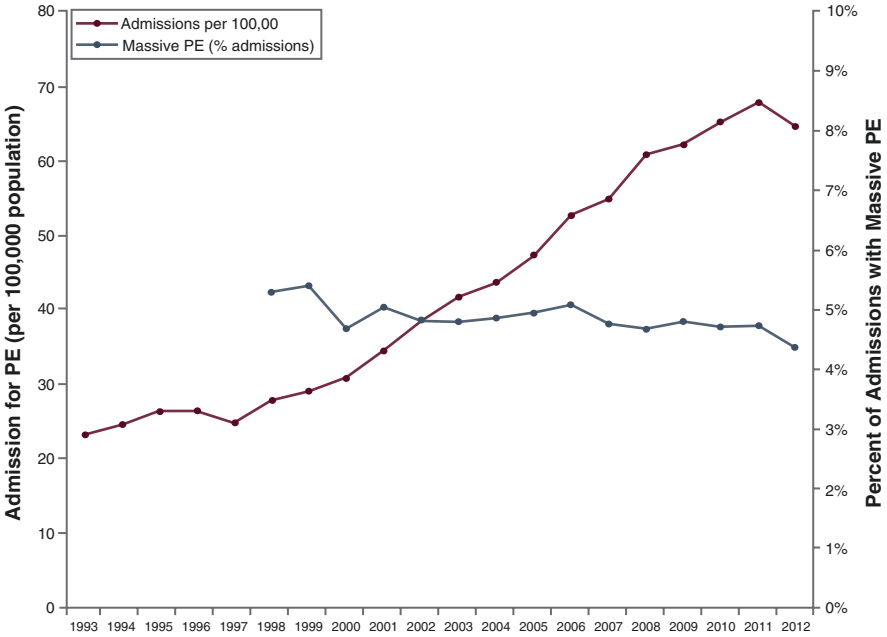

Fig. 1 Hospitalizations for PE from 1993 to 2012. Admissions for PE increased, while the percentage meeting criteria for massive PE decreased. PE pulmonary embolism. (Reproduced from: Chest. 2016; 150(1):35–45)

PERT

Background Patients with pulmonary embolism are diagnosed in the emergency department in 50% of cases. The severity of pulmonary embolism is typically then categorized into low, intermediate, or high risk. Low-risk patients, those who are hemodynamically stable without any evidence of right ventricular strain, can be discharged from the emergency department on anticoagulation alone with appropriate follow-up and have a very low risk of bleeding or recurrent venous thromboembolism [5]. Patients with high-risk pulmonary embolism have the highest mortality rates and present with hemodynamic instability. A significant proportion of patients present with intermediate-risk pulmonary embolism; they display hemodynamic stability but have evidence of right ventricular dysfunction or strain on presentation. These patients can go on to develop in-hospital hemodynamic collapse and death at estimated rates of 10% and 5%, respectively [6].

Objectives The goal of early risk stratification of intermediate and high-risk patients is to identify those at risk for decompensation and implement rapid interventions to prevent decline. Given the risk of imminent harm for these patients, intermediate and high-risk pulmonary embolism can be considered an in-hospital emergency. Furthermore, as outlined elsewhere, treatment options for these patients

are heterogeneous without an accepted algorithm for treatment or centralized location for care. These treatments require the coordination of multiple subspecialists and require time for implementation. In this environment of a mismatch between the patient needs and the clinical resources available, the PERT was created, following the previously established model of an in-hospital rapid response team to streamline patient care [7]. The objectives of the PERT encompass these concepts and aim to ensure a rapid response to patients with PE, provide the best-tailored therapeutic options to each patient while leveraging the input of multiple subspecialists and coordinating care among various services. Lastly, an organized system of patient identification, recording of data, and analysis of results will add volumes to the body of scientific knowledge surrounding the treatment of pulmonary embolism to improve patient care.

Design The initial design of the PERT, adopted at the Massachusetts General Hospital (MGH), will be described here [8] (Fig. 2). Since its inception, there have been many similar teams established across multiple institutions that have made modifications to this initial protocol based on their specific institutional needs and resources.

The PERT can be activated from any hospital unit – the emergency department, inpatient medical or surgical floors, intensive care units, or even outpatient clinics and outside referring hospitals, though in these settings the patient does need to be transferred to our institution for direct evaluation. The activation of the PERT is at the discretion of the immediate clinical provider, and there are no strict criteria for the severity of pulmonary embolism needed for activation. However, the multidisciplinary PERT discussion is typically reserved for patients who meet the criteria for intermediate or high-risk pulmonary embolism. The treating provider places a phone call to a centralized answering service where information regarding the patient is collected. This information is then sent via page to the on-call clinical fellow responsible for PERT activations. A simultaneous email is sent to an administrator to ensure accurate documentation of all activations for the purposes of prospective data collection.

Once the clinical fellow receives the referring provider's request for PERT evaluation, the fellow will collect pertinent clinical information about the patient, gather the available data, and request that the referring team obtain any additional appropriate testing.

After discussion with their attending physician, the clinical fellow organizes a multidisciplinary meeting to discuss patients with intermediate- and high-risk PE, and in certain cases of low-risk PE as well. This multidisciplinary discussion is done virtually via a commercially available web-based high-definition video conferencing tool [9]. Members of the group are notified via page about an upcoming meeting, and an email is sent with patient details and login information to the virtual platform. This platform allows participants to view the meeting organizers screen (i.e., the clinical fellow presenting the case) and listen and participate in the discussion via phone or directly through the application. Additional participants can also

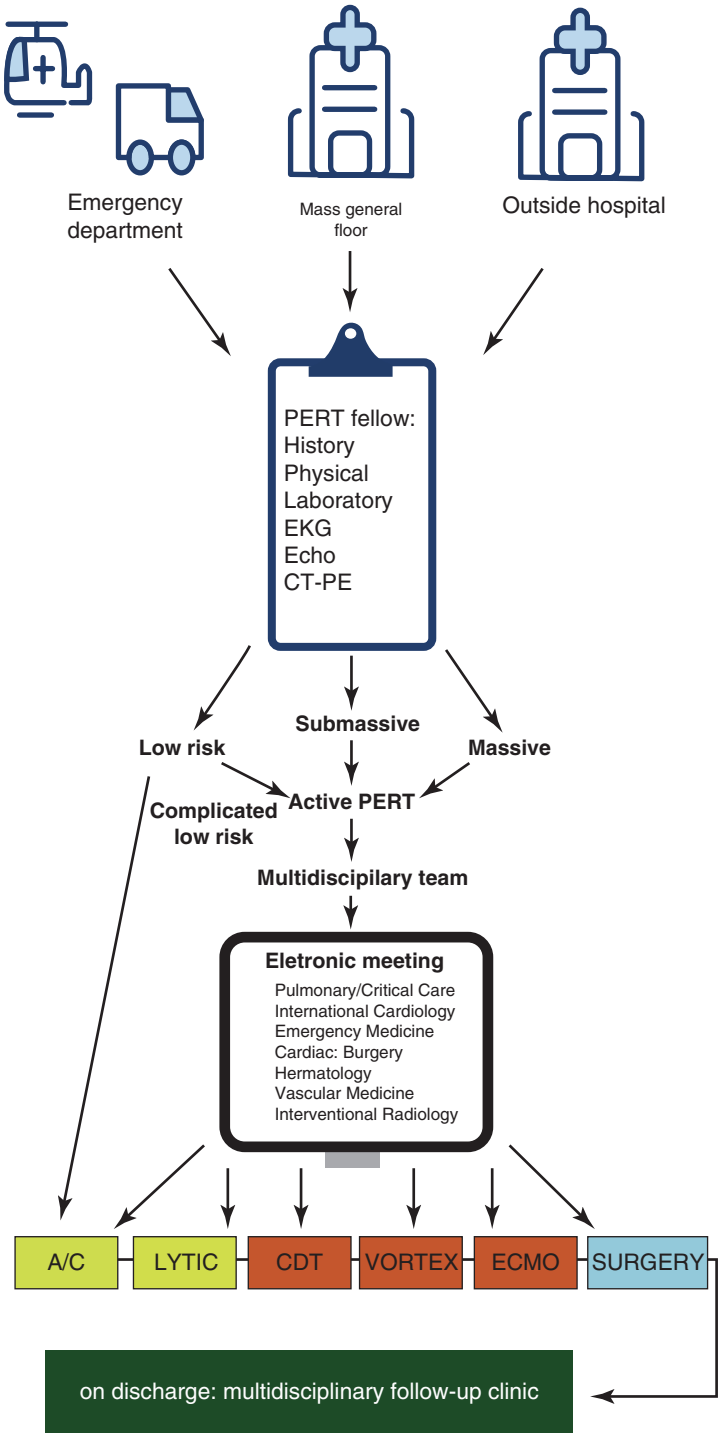

Fig. 2 Example of a PERT activation and workflow. (Reproduced from: Clin Chest Med. 2018; 39:621–630)

be included in the discussion, such as an oncologist who may be the longitudinal provider for a patient with a malignancy-associated pulmonary embolism, or an obstetrician for a pregnant patient with a pulmonary embolism [10].

At the completion of the meeting, the clinical fellow summarizes the recommendations generated by the multidisciplinary team. If a procedure or intervention is needed, the relevant members of the team implement this portion of the plan. The clinical fellow communicates the recommendations to the primary team and continues to follow the patient for the duration of their hospital stay. If at any time, the patient experiences a relevant clinical change related to their pulmonary embolism, another multidisciplinary meeting can be arranged.

Implementation As mentioned above, after the inception of PERT at Massachusetts General Hospital in 2012, rapid response teams for pulmonary embolism have been established at many institutions nationally and internationally. While all these teams share a similar goal of streamlining and delivering the best care to patients in a clinical area where high-quality randomized clinical trial data are lacking, each institution's PERT will be necessarily individualized. Robust data are lacking as to whether PERT improves patient outcomes, and there is similarly no specific PERT structure which has been shown to be superior to another. Thus, the formation of a PERT will need to take into account the specific needs and capabilities of the organization [11].

These specific considerations should include the assessment of the appropriate team composition (Fig. 3). PERT should include providers who are available for patient evaluation and triage, administration and implementation of medical therapy, interventional specialties that may be consulted for their endovascular or surgical skills, and providers who are able to participate in longitudinal patient care. A variety of specialists can perform the above functions, and the appropriate composition is dependent on the resources and availability of providers at the specific institution [12].

Additional institution-specific considerations should include guidance regarding how patients are identified and the PERT subsequently activated. It should be clear within this algorithm who is responsible for triage and initial clinical evaluation of the patient with pulmonary embolism. The mechanism for multidisciplinary discussion should be ascertained. In a survey of organizations in the National PERT™ Consortium, a minority utilized a virtual meeting software as described above, and were more likely to use a telephone conference call [13]. It should be determined at the time of development of the team which providers from the PERT will be responsible for immediate in-hospital follow-up and what the structure for long-term patient follow-up will be.

Institutions may consider developing a mechanism by which data are collected about patients for whom the PERT is activated. The purpose of this would be both for internal quality and safety review, as well as for study to ultimately contribute to the medical literature for this diverse group of patients. With the establishment of the PERT Consortium (see below), this type of data collection has become easier and more centralized.

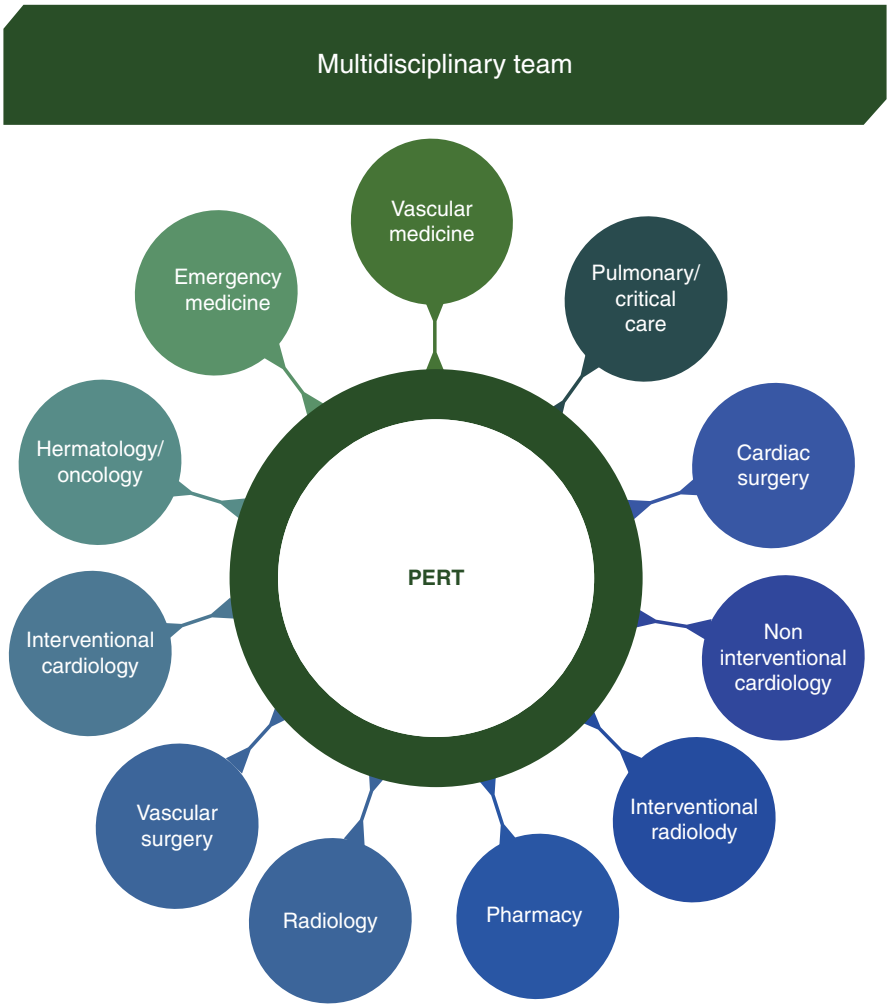

Fig. 3 Example of the composition or possible members of a multidisciplinary PERT. (Reproduced from: Clin Chest Med. 2018; 39:621–630)

Lastly, some consideration should be given to establishing quality metrics and goals that each individual PERT would like to maintain and achieve. As outlined by Galmer et al. [12], this could include metrics such as timing to therapeutic anticoagulation, performance of a comprehensive diagnostic workup, timely implementation of invasive therapies if indicated, and appropriate patient follow-up.

Clinical Follow-Up Shortly after inception, a multidisciplinary PERT follow-up clinic was established at MGH. Any patient for whom a PERT consult is placed is scheduled for an outpatient visit about 4–6 weeks after their initial consultation. The goal of this clinic is to improve the transition of care from the inpatient to the

outpatient setting. It is estimated that almost 50% of adults have some type of medical error at the time of their hospital discharge, and half of those patients experience an adverse event related to this error [14]. PERT follow-up clinic aims to reduce the issues that occur during these critical transitions of care and allows for a space to address these issues [15]. Patients and their provider can discuss additional testing needed for identifying a cause for the pulmonary embolism (occult malignancy screening, thrombophilia testing), monitoring and screening for long-term complications of the DVT/PE (chronic thromboembolic pulmonary hypertension, inferior vena cava filter retrieval), and clarifying anticoagulant management (specific agent, duration) [10]. To continue the multidisciplinary approach to patients seen in the outpatient follow-up clinic, providers meet for 1 hour prior to clinic to discuss a comprehensive treatment plan for patients to be seen that day.

Review of Published PERT Data

While the creation of PERT appeared to meet a glaring need of rapid multidisciplinary activation and decision-making for a severe illness with a high mortality rate, there is only limited published follow-up data exploring the effect of such teams on patient outcomes. With larger databases through the PERT Consortium (see below), large-level analyses will be possible to determine the best structure and design of a PERT, to determine the effect on patient care, and possibly to generate recommendations on the optimal workflow and interventions.

A review of the initial 30-month experience after the creation of the PERT at MGH was published in 2016 [16]. From an implementation and acceptance standpoint, this review demonstrated that the institution rapidly adopted the PERT model: there were 394 activations in the first 30 months, with a steady increase in the number of activations as time went on (Fig. 4). The majority of PERT activations originated in the emergency department, and 73% of patients already had a diagnosed PE at the time of activation of the PERT. The vast majority of consultations were for intermediate or high-risk PE (Fig. 5), and patients typically had significant clot burden (PE location noted as intracardiac, saddle, or in the main pulmonary artery for more than half of patients.). Most commonly, the PERT recommended anticoagulation alone, with only a small proportion of patients undergoing lytic or other invasive intervention (i.e., surgical thrombectomy), though at rates higher than previously published data. However, there was no increase in hemorrhagic complications in patients treated with catheter-directed lysis compared to patients who received anticoagulation alone. Mortality for massive pulmonary embolism at 30-day follow-up was 25% (Fig. 6).

More recently, additional data regarding the experience of PERTs nationally, internationally, and longer term data from MGH have been published [17–19]. The short-term experience nationally and internationally mirrors that of the initial experience at MGH. Data from the University of Kentucky suggested that activation of a PERT reduced ICU and overall length of stay, and despite an increased use of

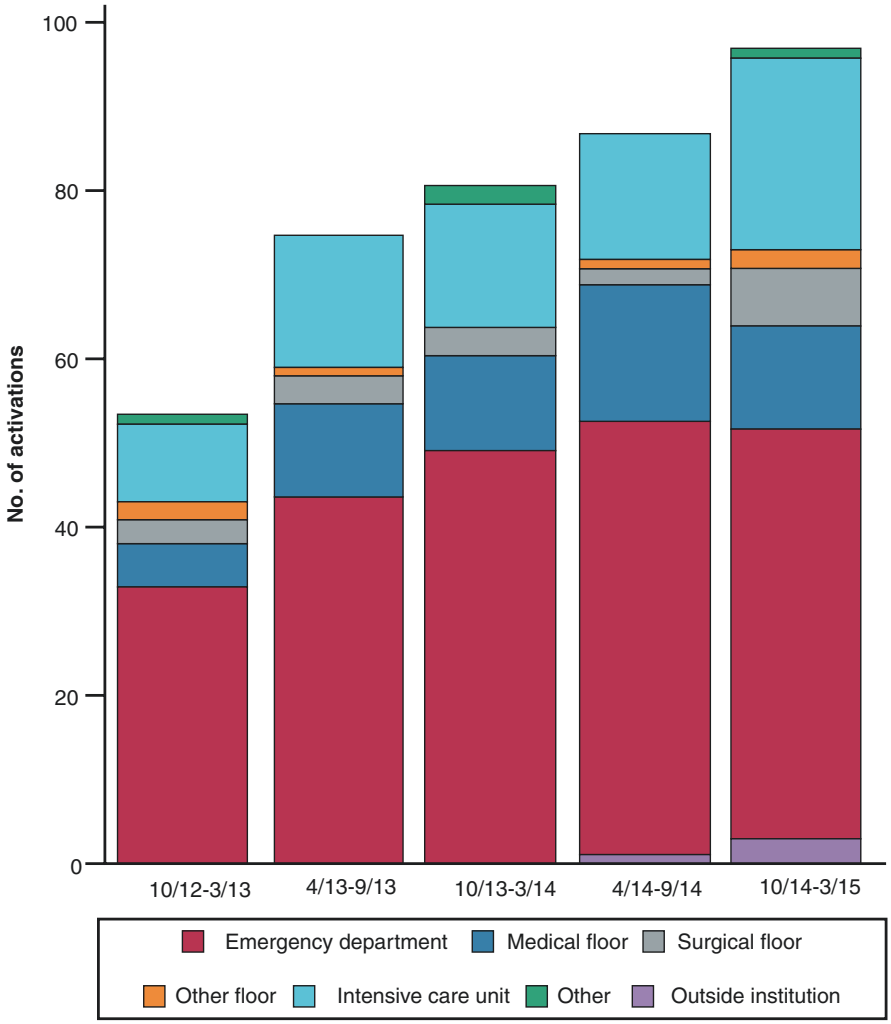

Fig. 4 PERT activations per 6-month interval since the team was established, organized by location of the activation, from the initial 30-month experience at Massachusetts General Hospital. PERT pulmonary embolism response team. (Reproduced from: Chest. 2016;150(2):384—393)

interventional techniques, there did not appear to be an increase in direct costs in patients for whom PERT was activated. In a cohort of patients in Singapore, it appears that activation of a PERT resulted in a reduction in the variation of care, more reliable reporting of parameters of right heart strain, reduction in ICU length of stay, shorter time to reperfusion therapy, and an increase in the use of reperfusion therapy without a change in hemorrhagic complications. Neither cohort revealed a change in short-term patient survival (30-day and hospital stay, respectively). A recent analysis from Cleveland Clinic compared clinical outcomes of patients with

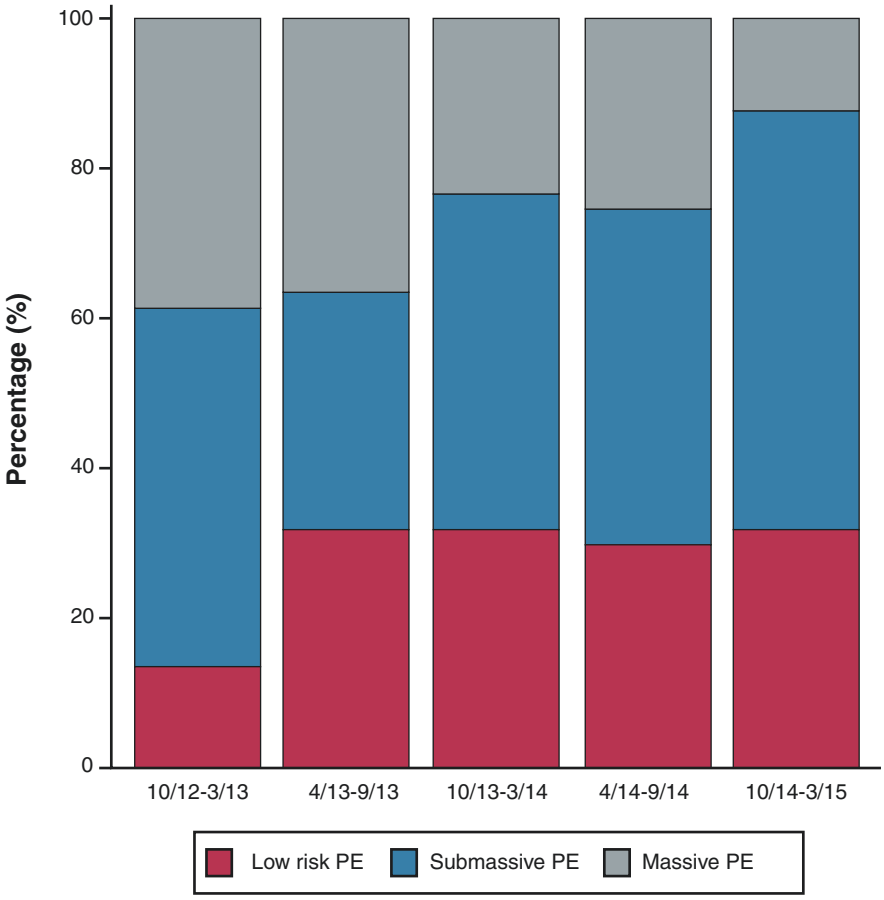

Fig. 5 Severity of pulmonary embolism in patients for whom PERT was activated, from the initial 30-month experience at Massachusetts General Hospital. PERT pulmonary embolism response team. (Reproduced from: Chest. 2016;150(2):384—393)

pulmonary embolism prior to and after the institution of PERT. After the creation of a PERT at this institution, patients with PE experienced less clinical significant bleeding, decreased IVC filter placement, a shorter time to therapeutic anticoagulation, and a significantly decreased 30-day or inpatient mortality. There was a non-statistically significant increase in the use of thrombolytics. All of these observations were more pronounced in patients with intermediate or high-risk pulmonary embolism [20].

Longer term, 10-year follow-up data were recently published from the MGH experience [19]. A total of 228 patients for whom the PERT was consulted were matched with 212 patients with pulmonary embolism at the same institution prior to the creation of the PERT. For the pre-PERT cohort, only patients who would have met the general criteria for PERT activation were included (large clot burden,

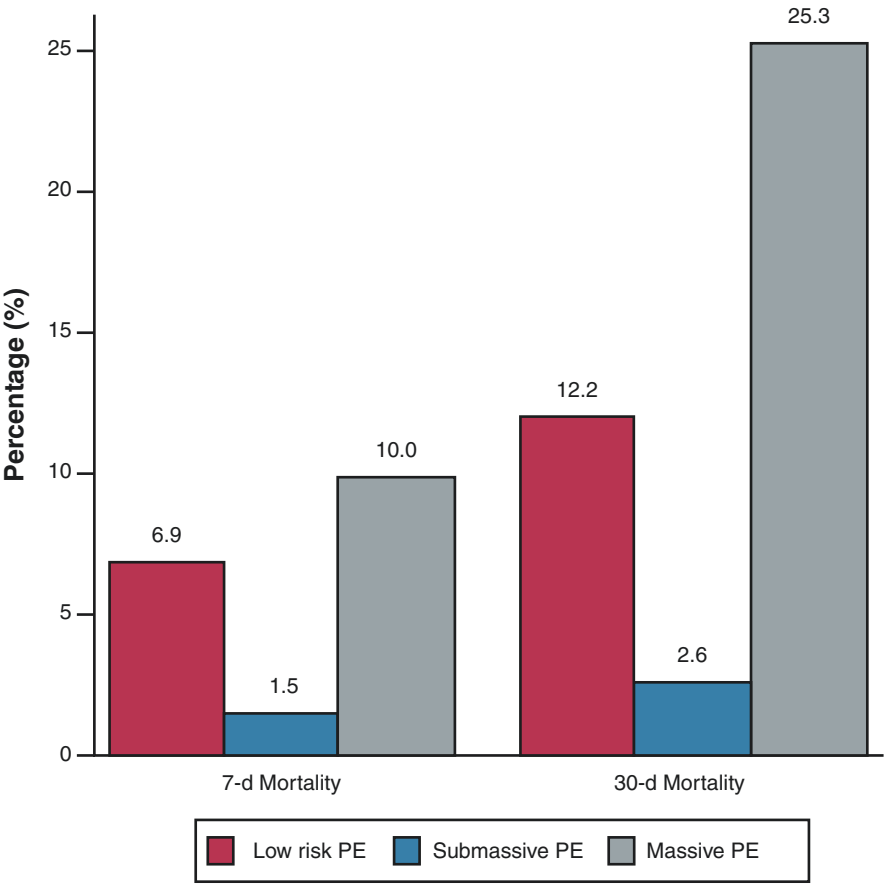

Fig. 6 Patient mortality at 7 and 30 days after PE diagnosis, group according to PE mortality, from the initial 30-month experience at Massachusetts General Hospital. PE pulmonary embolism. (Reproduced from: Chest. 2016;150(2):384—393)

tachycardia or hypotension or hypoxemia, or evidence of right heart strain based on biomarkers, or transthoracic echocardiogram). The post-PERT cohort of patients had a similar proportion of massive or high-risk pulmonary embolism, but the proportion of intermediate-risk PE increased while low-risk PE decreased (Fig. 7). While the rate of systemic thrombolysis and surgical thrombectomy were the same in both cohorts, more patients in the post-PERT era underwent catheter-directed therapy (Fig. 8). The clinical outcomes of these patients were similar, however, despite an increase in catheter-directed therapies in a subgroup of patients after the creation of PERT. Across both groups, the rate of major bleeding complications was similar at 30-day follow up, as was 30-day mortality. Thirty-day mortality remained the same between groups after adjusting for PE severity. These long-term data suggest that the implementation of a PERT results in an increased use of advanced

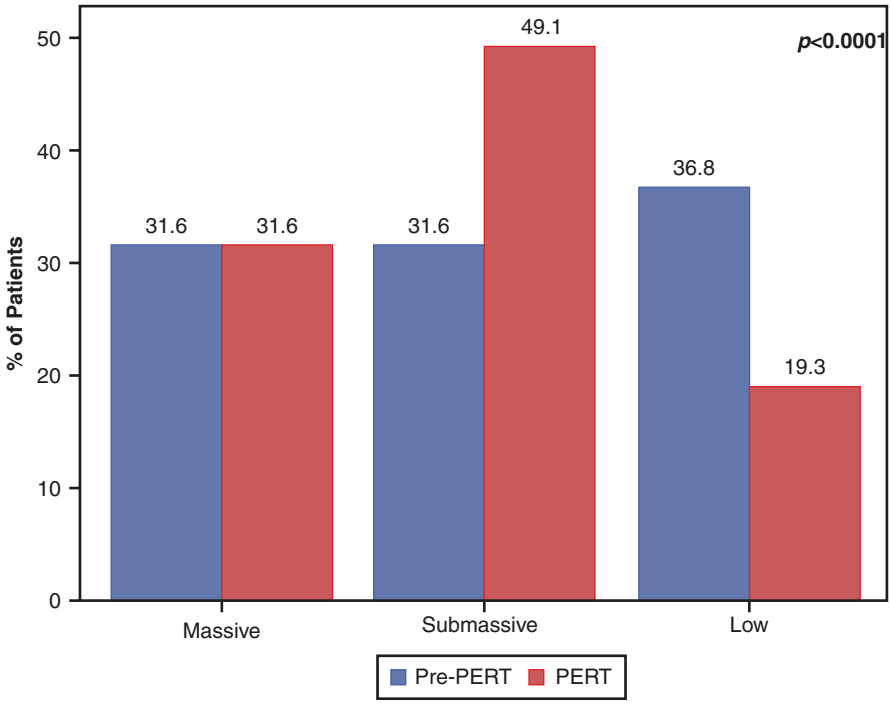

Fig. 7 Severity of pulmonary embolism in a pre-PERT cohort of patients compared to a 10-year analysis of patients after the creation of PERT at MGH. PERT pulmonary embolism response team. MGH Massachusetts General Hospital. (Reproduced from: J Thrombosis and Thrombolysis. 2019. 47:31–40)

therapies, and that this occurs mostly in patients with intermediate-risk pulmonary embolism. It also appears that there is no increase in major bleeding and no change in mortality as a result of these interventions. More research is needed to determine if there are outcomes that are improved as a result of this PERT intervention and the increased use of catheter-based therapies. Additional study into longer-term clinical outcomes, patient and provider satisfaction, impact on healthcare costs, and resource utilization, among other considerations, is necessary to understand the impact these teams have on patients and the institutions where they are formed.

PERT Consortium

The PERT Consortium was created in 2014 and is a 501c3 nonprofit organization. In 2015, the first annual meeting of the PERT consortium was held in Boston, MA. There are currently more than 90 member institutions in the Consortium. The goal is to promote the PERT model in healthcare institutions throughout the

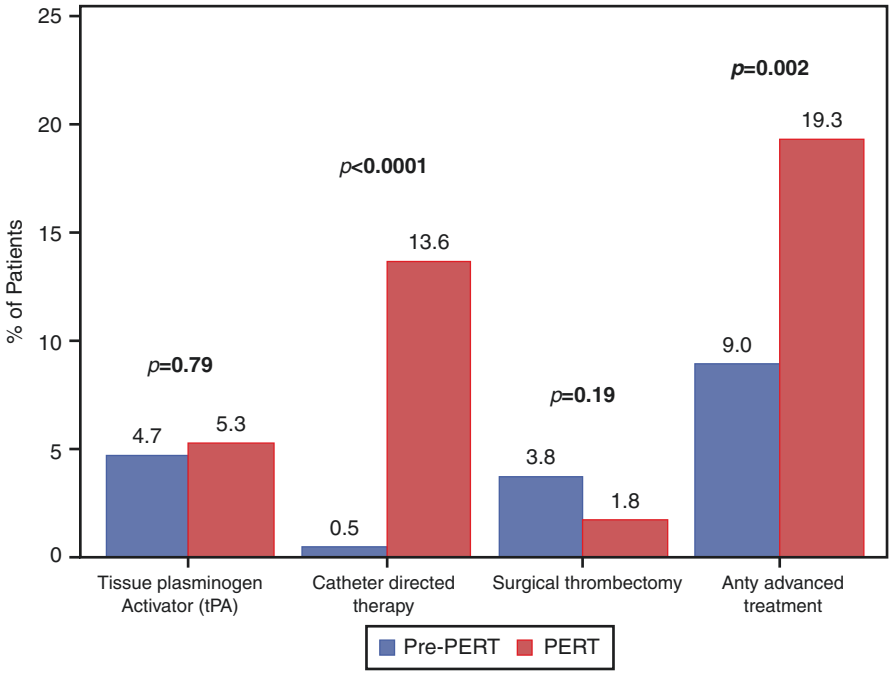

Fig. 8 Distribution of the types of therapies/interventions for pulmonary embolism prior to the creation of PERT compared to a 10-year time period after the institution of a PERT at MGH. PERT pulmonary embolism response team, MGH Massachusetts General Hospital. (Reproduced from: J Thrombosis and Thrombolysis. 2019. 47:31–40)

country, expand and guide the study of pulmonary embolism, and create a centralized location for information about PE evaluation and treatment for the general public and for healthcare providers [21]. The PERT Consortium organization contains several committees: the Clinical Practice and Protocol Committee, Communication Committee, Development Committee, Education Committee, Governance Committee, and Research Committee. Each committee has specific aims and goals to promote the understanding and treatment of pulmonary embolism, as well as to manage and organize this multi-institutional collaboration. This organization creates an exciting platform for the design and implementation of multicenter clinical trials in the field of pulmonary embolism.

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Post-PE Management

William B. Graham and Victor F. Tapson

Introduction

The care of a patient who has suffered from acute pulmonary embolism (PE) continues after discharge from the hospital. While the focus of this text is PE, deep venous thrombosis (DVT) and PE represent the spectrum of one disease, and the two must be considered together. In the clinic, a number of decisions remain including resolution of symptoms, anticoagulation risk/benefit and dosing, whether to consider thrombophilia testing or surveillance for recurrent venous thromboembolism (VTE), and ultimately monitoring for chronic thromboembolic disease. Due to the heterogeneity of the PE patient population and the continuously evolving evidential landscape in the post-PE setting, published guidelines and specific protocols for many aspects of care are lacking. This may create uncertainty for the clinician when counseling patients and making treatment decisions. The objective of this chapter is to provide a framework for post-discharge PE care by which the advanced care provider, primary care physician, or specialist can provide a personalized and patient-centered approach using the best available evidence.

Mortality, recurrent VTE, and complications from acute PE are most common in the immediate post-PE period [1]. It is therefore ideal for the patient to be seen in clinic within approximately 2–4 weeks after discharge. The first visit is not only a crucial time to assess the patient's recovery from the PE but also serves to lay the foundation for a durable patient–provider relationship.

Our chapter overlaps slightly with others; although we offer some comments about anticoagulant selection and duration – a key component of post-PE follow-up – this will be covered comprehensively in another Chap. 5. An important aspect of PE follow-up is cautious observation for symptoms, signs, and other evidence of

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chronic thromboembolic pulmonary hypertension (CTEPH). We offer some information in this realm, but CTEPH is also covered comprehensively in a separate Chap. 12.

The Outpatient Clinic Setting – Follow-Up After Acute PE

Patients who have experienced acute PE or DVT require comprehensive follow-up. Hematologists, pulmonologists, and cardiologists often follow patients after a PE, but depending on their training and experience, may not have the expertise for complex decisions in this area. While follow-up by the primary care clinician is important, research in this field continues, and the evidence base is evolving. An excellent example of this is the advent of low-dose anticoagulation based upon the EINSTEIN CHOICE and AMPLIFY EXTEND trials [2, 3]. Treatment for inoperable CTEPH is also evolving with recently approved medical therapy (riociguat) and recently completed promising trials (macitentan), as well as the evolving success of balloon pulmonary angioplasty (BPA) [4–6]. Other questions must be addressed at some point after the thromboembolic event. Under what circumstances should a patient with PE and paradoxical embolism have a PFO closed? Should an inferior vena caval (IVC) filter in place for 10 years be removed? Should imaging be repeated? Clinicians need to be aware of new research and evolving data and be able to answer complex questions based on experience when the evidence base is inadequate. Thus, we believe that follow-up with specialists in the field of VTE is essential. If a clinic does not have a PE expert who has extensive experience, then a multidisciplinary clinic may be the ideal way to guarantee appropriate follow-up. Evolving anticoagulation data, expertise in CTEPH, and post-thrombotic syndrome are just a few reasons why expertise in PE follow-up is crucial. Consultation with experts is critical when a PE clinic is not available. At Cedars-Sinai, our PE clinic is fed from the inpatient consults made to the PE response team (PERT); this team consults on these patients and follows them through their hospitalization and then in clinic for long-term follow-up. Table 1 lists key issues to consider early in the outpatient post-PE setting.

Symptoms

It is essential on the first and subsequent visits to evaluate symptoms and trends since the index event. Because symptoms may take weeks or longer to resolve, they may remain present at the first post-discharge visit. Trends are important: pain from pulmonary infarction nearly always resolves in less than 1 week, whereas resolution of dyspnea may take longer. Persistent exertional dyspnea is the principal symptom of ongoing cardiopulmonary stress due to PE, and residual dyspnea may be present within the first month after the diagnosis of acute PE. However, at the

Table 1 General considerations at first outpatient post-PE visit

Symptoms
Characterization of VTE event, review imaging when applicable
VTE risk factors
Bleeding risk factors
Review family history
Anticoagulation compliance
Anticoagulant side effects
INR (if applicable)
Drug interactions
Discuss thrombophilia testing (if applicable)[a]
Plan IVC filter removal
Appropriate activity level
Pulmonary or cardiac rehabilitation in relevant cases
Physical examination/complete blood count
O_2 saturation at rest/exercise (consider 6-minute walk)
At 3 month visit – plan imaging if symptomatic at 3 months

Abbreviations: *PE* pulmonary embolism, *VTE* venous thromboembolism, *INR* international normalized ratio, *IVC* inferior vena caval filter, *APS* antiphospholipid antibody syndrome

[a]Testing should be delayed until 3 month visit, and done off anticoagulation if possible. Triple-positive APS (and possibly APS with venous + arterial events) is the only thrombophilia that could potentially affect the specific choice of anticoagulant)

first visit to clinic, chest pain, syncope, dizziness or near syncope, and palpitations should have completely resolved. If not, a careful reevaluation should be undertaken. Pain and swelling from residual DVT may take weeks depending on the extent of the clot, and in some patients may not resolve but instead evolve into the chronic entity of post-thrombotic syndrome. Near syncope and syncope when present should have resolved prior to discharge – these are extremely concerning if persistent.

It is important for the patient to be aware of the variability in which recurrent DVT or PE could present; a recurrent VTE event may present completely different from the initial event. Because the symptoms of DVT and acute PE are nonspecific, patients should understand that, for example, what appears to be a pulled muscle might be recurrent DVT, and that pleuritic, musculoskeletal-type pain in the back or lateral chest might actually represent recurrent PE with infarction. Dyspnea or syncope might be mistakenly blamed on underlying chronic cardiopulmonary disease such as asthma, chronic obstructive pulmonary disease (COPD), or congestive heart failure. It should be understood that sudden onset palpitations or proven atrial fibrillation might be triggered by acute PE. Acute PE is sometimes misdiagnosed as a panic attack, anxiety, or a viral illness and patients with prior PE should understand the potentially protean presenting manifestations of a potential recurrence. When possible, accompanying family members should also be educated. Symptoms of DVT and PE should be carefully reviewed with patients prior to discharge and reinforced at clinical follow-up.

History: The Initial Event

We believe that a visit within the first few weeks after diagnosis is essential. We routinely schedule patients for a 3-month and 6-month visit; these are often critical time points for anticoagulation decisions. We then schedule return visits every 6–12 months realizing that needs may vary among patients. The first visit after the acute VTE event should start by obtaining a complete history that includes the sequence of events leading to the PE diagnosis. A key question is whether the event was provoked or not – this is often not a straightforward issue. It is important to realize that acute DVT and PE represent the spectrum of one disease and follow-up for both entities overlap.

The hospitalization should be reviewed – if there is any doubt about the diagnosis, the actual radiographic images should be reviewed. Was the diagnosis of acute PE certain? Is there evidence of associated chronic PE based upon symptom evolution, chest computed tomographic angiography (CTA), or a disproportionately elevated estimated PA pressure by echocardiography? Patients may present with acute PE but with a higher than logical echo-based estimated PA pressure. If so, is this from comorbid cardiopulmonary disease or in fact due to acute on chronic PE? If care was provided at a referral hospital, an effort should be made to obtain the records and diagnostic images (particularly chest CT, VQ scan, and echocardiogram) or at least the reports and have the information incorporated into the patient's medical record. The utility and interpretation of laboratory testing including thrombophilia testing is touched upon later in this chapter, and in detail elsewhere in this volume.

Risk Factors for VTE

The clinician should establish the potential risk factors for the thromboembolic event, based upon Virchow's triad of reduced mobility, venous injury, and hypercoagulability [7]. Recent surgical or other invasive procedures, trauma, recent travel, level of activity, and exercise tolerance prior to the onset of symptoms should be reviewed. Proven or possible cancer or other obvious underlying medical illnesses should be considered.

A family history of VTE events or miscarriages in a first-degree relative under age 50 may suggest an underlying inherited thrombophilia [8]. When inquiring about the patient's personal and social activities, it is also important to ask about smoking habits, as tobacco smokers with a 20 or greater pack-year smoking history have an increased risk of VTE [9–10, 11]. Interestingly, animal studies have found that mice exposed to e-cigarette vapor have increased platelet activation and shortened thrombosis times compared to controls [12]. While no prospective studies in humans have been conducted to determine if vaping is a risk factor for VTE, further research is required into the health impacts of this increasingly popular behavioral

trend [13]. Risk factors or lack of them, including prior VTE, will impact on the duration and potentially the intensity of anticoagulation therapy, and even the specific anticoagulant prescribed. Commonly, less established provocative features may be present such as less invasive surgical procedures or extended air or ground travel in otherwise risk-free patients. A patient with, for example, a 4-hour flight or minor knee arthroscopy as the only evident risk factor should suggest a particular susceptibility, that is, "minimal provocation." While patients with acute PE often have comorbid conditions, it is not always clear how these impact on the risk of VTE and whether they constitute a "provoking entity." Inflammatory bowel disease and active cancer increase the risk for acute VTE [7]. COPD, for example, may not, unless it has a significant impact on the patient's mobility. Many associated comorbidities increase morbidity and mortality associated with acute PE (Table 1). A careful risk assessment is essential but clear decisions about therapy cannot always be strongly evidence based. Many patients cannot be simply grouped as provoked or unprovoked.

Assessment of Bleeding Risk

At the first and all return visits, it is important to ask about fatigue, melena, easy bruising, or other symptoms that could suggest supratherapeutic anticoagulation or occult hemorrhage due to anticoagulation. Based upon the variability of bleeding sequelae, a detailed history is important. In addition, an assessment of bleeding risk should be undertaken – anticoagulation duration and intensity are predicated upon a careful overall risk–benefit assessment. Decisions regarding IVC filter placement must be made if anticoagulation is deemed otherwise imperative, but the bleeding risk is assessed as too high.

Medication Review

A complete review of medications is essential at all post-PE clinic visits. The appropriate dose and frequency of anticoagulant should be reviewed. The provider should consider discontinuing any nonessential medications and supplements that are associated with an increased bleeding risk, as well as medications with known drug–drug interactions with the anticoagulant prescribed. Concomitant nonsteroidal anti-inflammatory agents, for example, should be avoided unless short-term use is essential. Curcumin, the polyphenol responsible for the yellow color in the curry spice turmeric, has anticoagulant properties. This substance and its derivative, bisdemethoxycurcumin, may inhibit clotting factors and cause bleeding [14]. Other supplements that may also increase the risk of bleeding are listed in Table 2. Innumerable warfarin drug interactions have been described, and patients must realize that any new medication must be scrutinized. Drug interactions are discussed in more detail below.

Table 2 Supplements potentially associated with increased bleeding risk

Turmeric	*Ginkgo biloba*
Dong quai	Ginseng
Feverfew	Ginger
Garlic	

Prothrombotic medications such as hormone-based oral contraceptives or androgen replacement therapy should be reviewed. Should oral contraceptives be discontinued? While it may be wise to minimize the dose, as long as a patient is anticoagulated, the risk of recurrent VTE on continued estrogen therapy appears to be low. If anticoagulants are discontinued, lower risk birth control options such as the progestin-only pills, the implant, and the hormonal intrauterine device generally do not increase a person's risk of DVT, PE, or stroke [15–19].

Testosterone has been a popular supplement for individuals with the goal of muscle building, and there appears to be an inherent risk of vascular events, such as PE, with testosterone use [20]. While the mechanism is unclear, there is evidence of an association between testosterone therapy and increased platelet aggregation, increased thrombus-promoting receptor expression on platelets, and polycythemia [20]. The risk is likely higher when polycythemia develops, and the risk appears to be lower when used as replacement therapy than it is with supplemental enhancement therapy. The risk of VTE events is even more unclear with non-FDA-approved herbal supplements marketed as testosterone enhancers, such as Fenugreek extract, for example [21].

Physical Examination and Laboratory Testing

Physical Examination

A focused physical exam should be done on the first and subsequent clinic visits. Neither tachycardia, tachypnea, hypotension, nor oxygen saturation of <90% should still be present at the initial visit. If present, and not due to comorbid chronic disease, they are an indication of ongoing hemodynamic stress and should be addressed with urgency. We routinely test the O_2 saturation with ambulation post discharge; hypoxemia solely from acute PE is rarely present by the first post discharge visit. In the absence of cardiopulmonary comorbidities, the lung and cardiac exams are generally normal by the first clinical follow-up – a pleural rub and/or focal tenderness between the ribs from pulmonary infarction generally lasts less than a week. In patients with residual DVT, leg swelling or tenderness may still be present and should be monitored. A careful skin and musculoskeletal exam may reveal bruising, petechiae, edema, skin changes from anticoagulation, chronic venous stasis, focal panniculitis (erythema nodosum), or Raynaud's phenomenon. In the relevant clinical setting, these may be indicators of an occult prothrombotic or inflammatory state or connective tissue disease.

Laboratory Testing

Laboratory screening on the first visit and subsequent visits can be limited to a few commonly available tests. The hemoglobin/ hematocrit should be measured to assess for occult blood loss after starting anticoagulation. An abnormally elevated hematocrit or platelet count may also raise concern for underlying polycythemia or essential thrombocytosis. Conversely, a chronic or persistent anemia or leukopenia may be an indication of rarer problems such as myelodysplastic syndrome, or paroxysmal nocturnal hemoglobinuria (PNH), a condition in which half of all deaths are caused by VTE [22, 23]. The serum creatinine is critical for low-molecular-weight heparin (LMWH) and direct oral anticoagulant (DOAC) use and dosing. Troponin and brain natriuretic peptide (BNP) levels are helpful in risk-stratification at the time of PE diagnosis; however, they are not routinely checked in the clinic unless there is clinical suspicion of chronic PE with present or evolving pulmonary hypertension, or ongoing cardiac ischemia or decompensated heart failure. Thrombophilia testing, if indicated, is usually reserved for subsequent clinic visits, and for certain of these is best performed off anticoagulation; this is discussed in more detail later in this chapter as is screening for occult malignancy.

Anticoagulation Post-Pulmonary Embolism

Anticoagulation and relevant clinical trials are covered in detail in a separate Chap. 5, but a few key points are made below, as this is a primary consideration in the post-PE setting. The paradigm of VTE treatment has been transformed by the introduction and widespread use of the DOACs. Indeed, the recent guidelines by the American College of Chest Physicians (ACCP) recommend DOACs as first-line therapy for the management of most patients with VTE [24], and the majority of PE patients discharged after an inpatient stay or directly from the emergency department are prescribed a DOAC [25]. Contraindications to the use of DOACs include pregnancy (inadequate data), breast feeding, mechanical heart valves, and triple-positive APS VTE. The latter is discussed below under "thrombophilia testing."

Drug Interactions

At post-PE clinic visits, all medications should be carefully scrutinized. Innumerable drug interactions can occur with warfarin; even intermittent medications such as acetaminophen may affect the international normalized ratio (INR) [26]. The DOACs are impacted by far fewer interactions than warfarin. Transcellular transport of the DOACs is dependent on p-glycoprotein mechanisms, and the DOACs rivaroxaban and apixaban require CYP3A4-mediated pathways for metabolism.

They should not be prescribed with known strong CYP3A4/p-glycoprotein inducers or inhibitors [27, 28]. Importantly, supplements such as St. John's Wort are often not included on a patient's medication list – this drug is a potent CYP3A and P-gp inducer and will result in subtherapeutic DOAC levels. Certain anticonvulsants as well as rifampin may have the same effect. Certain antifungals and the early HIV therapies (protease inhibitors) are among the drugs that are strong CYP3A and P-gp inducers and will result in supratherapeutic DOAC levels. The DOACs are discussed in more detail in a separate chapter [27, 28].

Renal and Hepatic Insufficiency

Hepatic impairment and renal failure are relative contraindications; both are associated with an increased risk of bleeding. It has been recommended that DOACs be avoided in moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy. Early data suggest that DOACs may be safe in patients with mild to moderate chronic liver disease [29].

It is recommended that rivaroxaban not be used for acute VTE if the creatinine clearance is less than 30 mL/min [30]. Apixaban is less renally metabolized, and thus, a lower creatinine clearance can be considered [30]. Recent data suggest that apixaban 5 mg twice-daily may be a safe option in atrial fibrillation patients with chronic and even end-stage renal disease (ESRD) on dialysis [31, 32]. A dose reduction to 2.5 mg has been recommended when used for stroke prevention in atrial fibrillation in frail, elderly patients with chronic kidney disease (<60 kg in weight, >80 years of age, serum creatinine >1.5) [32]. These studies do provide a foundation to support the use of apixaban for DVT/PE treatment in patients with impaired renal function; however, currently there are inadequate data to allow a recommendation for ESRD in this population. Clinicians following patients in the post-PE setting on apixaban with severely reduced creatinine clearance need to make carefully calculated decisions and in general, use warfarin until more data are available. For both dabigatran and edoxaban, the dose can be decreased in patients with reduced creatinine clearance, but there are no recommendations for ESRD [27].

Obesity and Anticoagulants

Obesity is common comorbidity affecting patients with PE, and the large DOAC clinical trials also excluded patients with extreme obesity, although patients >100 kg were included [33–36]. This considerably influenced the 2016 guideline statement by the International Society of Thrombosis and Haemostasis (ISTH), which advised against the use of DOACs in patients with a BMI exceeding 40 kg/m^2 or a weight in excess of 120 kg [37]. However, a recent review found that standard 20 mg rivaroxaban dosing has comparable plasma concentrations and factor Xa inhibition in

patients who weigh greater than 120 kilograms [38]. For practical purposes, if there is concern for insufficient anticoagulant effect in an obese or overweight patient on an anti-Xa DOAC, an anti-factor Xa assay (specifically calibrated for that DOAC) may have utility. If the level is low, the anticoagulant should be switched to an alternative agent, generally warfarin, which would have better absorption or bioavailability in this setting.

Anticoagulant Absorption and Bariatric Surgery

Individual characteristics of the post-PE patient must be addressed. Bariatric surgery is one such concern. Mechanisms of malabsorption include reduced surface area for drug absorption, decreased length of intestine and drug transit time, changes in pH affecting drug dissolution, and the bypass of drug transporter locations [39]. Overall, the changes in medication absorption are primarily related to alteration of drug pharmacokinetics due to anatomic changes.

Warfarin is predominantly absorbed in the proximal jejunum and ileum and binds extensively (97–99.9%) and nonspecifically to plasma proteins with only a small percentage of the drug free in circulation to exert its biologic effects. Long-term warfarin patients require a postoperative dose reduction of ≥20%, especially for Roux-en-Y gastric bypass procedures [40]. It has been suggested that the observed elevation in INR and increased sensitivity to warfarin are due primarily to reduced gastric acid and drug absorption [41].

Absorption of rivaroxaban occurs in the gastric pylorus, whereas apixaban is primarily absorbed in the first and second portions of the duodenum. Edoxaban is primarily absorbed in the upper gastrointestinal tract, with approximately 13% absorbed in the colon [42]. Dabigatran etexilate is a prodrug with low bioavailability (approximately 6.5%) and its absorption in the stomach and small intestine is dependent on an acid environment. The original DOAC trials excluded patients who had previously undergone gastrointestinal surgery. Patients with prior Whipple surgery, or similar procedures involving the distal stomach/duodenum, may have impaired anticoagulant absorption, particularly if prescribed one of the DOACs. Current literature is limited to case reports of failures (or success) with the use of DOACs following these gastrointestinal procedures, and therefore they should be used cautiously [42]. Less information is known about absorption after various bariatric surgeries such the Roux-en-Y gastric bypass, lap band, or gastric sleeve resection. More data are needed in this realm.

Cancer and Anticoagulants

Specific hypercoagulable conditions may necessitate a particular type of anticoagulation; details are offered in Chapter "Treatment for Pulmonary Embolism: Anticoagulation Selection and Duration" (Anticoagulation Therapy). Venous

thromboembolism due to malignancy is one condition in which LMWH has been considered the standard of care, based on superiority to warfarin [43]. However, this has been challenged by the recently published SELECT-D trial, which showed that VTE recurrence occurred more frequently in cancer patients who were treated with dalteparin than rivaroxaban (11% dalteparin group, 4% rivaroxaban group) [44]. A significantly higher rate of clinically relevant nonmajor bleeding was seen in patients anticoagulated with rivaroxaban (13%, compared to 4% in dalteparin group), particularly in patients with gastrointestinal malignancy. In addition, among patients with cancer-associated VTE, edoxaban reduced the risk of recurrent VTE but increased the bleeding risk compared to dalteparin. Finally, a more recent trial demonstrated that oral apixaban therapy was associated with very low rates of bleeding and significantly lower VTE recurrence with superior quality of life outcome measures compared to parenteral dalteparin in the treatment of cancer-associated VTE (ADAM VTE) [45]. Based on available data, it would be prudent to use DOACs cautiously in patients with an underlying gastrointestinal malignancy. Shared decision making between the patient and provider, with a discussion of risks and alternatives, should guide the choice of which anticoagulant is used.

Duration of Anticoagulation: Persisting Risk of VTE and Thrombophilia Testing

Duration of Anticoagulation

Duration of anticoagulation is covered in detail a separate chapter. We will make a few key comments, since this is a critical area in post-PE patients. The risk of VTE recurrence is generally low if VTE is provoked by surgery, intermediate if provoked by a nonsurgical risk factor, and high if unprovoked. These risks affect whether patients with VTE should undergo short-term vs indefinite treatment [24, 46]. However, patients undergoing surgery, for example, are a heterogeneous group, and the presence of additional risk factors should always be considered when determining duration of anticoagulation.

Patients with acute VTE require anticoagulation for a minimum of 3 months, with some requiring longer periods, depending on initial and ongoing risk factor assessment. The rationale for indefinite anticoagulation is based upon randomized trials and meta-analyses suggesting that prolonged anticoagulation reduces the rate of VTE recurrence [24 , 46, 47]. Long-term epidemiologic studies of recurrence risk support this concept. However, the reduction in VTE recurrence seen with prolonged anticoagulation is achieved at the expense of an increased risk of bleeding making a careful assessment critical. Appropriate anticoagulation duration may or

may not be obvious at the first visit after the acute PE event. Our approach to selecting those likely to have a favorable risk-benefit for more prolonged anticoagulation is discussed in the sections below.

A critical decision facing the clinician is whether to classify a PE event as provoked or unprovoked, although this is not as clear-cut as it might seem. VTE occurring after major surgical procedures, or after hip fracture or multiple trauma, may be the clearest provoked scenarios. VTE events are infrequent in these individuals with appropriate prophylaxis but may still develop during or after discontinuation of prophylaxis. Indefinite anticoagulation should be strongly considered in the setting of recurrent provoked VTE, or provoked VTE with persistent, or multiple major risk factors (e.g., active cancer or APS) [24]. Patients with events that may seem triggered by an event like a long flight or automobile ride might be considered "minimally provoked" and more prolonged anticoagulation than 3 months strongly considered. Whether the size of the thromboembolic event, its effect on blood pressure or right ventricular function, or the presence of residual DVT at the time of the PE should impact on duration of therapy is unclear [48, 49]. For example, there are no clear guidelines on how long to treat massive acute PE, but our group has been inclined to treat these patients for at least 6 months even when provoked, and as always, be certain than symptoms fully resolve. Furthermore, a small and/or incidental PE may also be unprovoked or associated with strong risk factors for recurrence. Whether a subsequent event could, for example, present as fatal PE may not be predictable.

The risk for recurrent VTE is highest in the first month following the index event [1]. For this reason, it is essential to advise the patient to carefully monitor symptoms in the first few weeks and ensure close follow-up after discharge from the hospital. Approximately 30% of all patients with VTE will have recurrence within a 10-year period when off anticoagulation [50]. A multitude of studies have investigated whether biochemical markers like D-dimer are helpful in predicting risk for recurrent VTE after discontinuation of anticoagulation. Indeed, two meta-analyses confirmed that an elevated D-dimer level 1 month after completion of anticoagulation is associated with a significantly increased risk for VTE [51, 52]. The DASH prediction model is a validated clinical risk prediction score that is used to calculate the risk of recurrent VTE after anticoagulation has been discontinued. Variables used in the risk model include male gender, an elevated D-dimer measured 1 month after stopping anticoagulation, and age < 50 years of age. Patients who meet all risk criteria have a 19.9% annual risk of recurrence and may warrant longer if not indefinite anticoagulation [53].

In 2008, the HERDOO2 rule was published, based upon a prospective multicenter cohort study of 646 patients with a first, unprovoked VTE treated with short-term anticoagulation [54]. No predictors for a low risk of recurrence were found in men, but in women, a low-risk group was identified. One point was given to patients with either hyperpigmentation, leg edema, or redness of either leg. One point each was also assigned for BMI > 30 kg/m^2, age > 65 years, or a D-dimer ≥ 250 μg/L

while anticoagulated. It was concluded that women with unprovoked VTE with a HERDOO2 score of 0 to 1 could discontinue anticoagulation, while women with a score of at least 2, and all men, should continue.

Subsequently, 2785 subjects (44.3% female) with first unprovoked VTE (proximal DVT or PE) who had completed 5–12 months of anticoagulation were enrolled at 44 medical centers in seven countries in an effort to validate the HERDOO2 score [55]. In low-risk women who discontinued anticoagulation, VTE recurrence per patient-year was 3.0%, and in high-risk women who discontinued anticoagulation, VTE recurrence per patient-year was 7.4%. In high-risk women and men who continued anticoagulation, it was 1.6%. Of note, when applied, the HERDOO2 score appears to only have validity using the VIDAS® D-dimer assay [56].

In our post-PE clinic, we do not routinely use the HERDOO2 score for decision-making on length of anticoagulation in women with a history of unprovoked VTE. Patients in the trials were followed for only 12 months. Available data have not clearly established that the predictors identified in the HERDOO2 cohort are universal predictors of recurrence in women. Furthermore, our experience over the past 25 years has simply been that women *without* the features included may still be prone to recurrence. A patient with an elevated D-dimer while on anticoagulation as her only HERDOO2 feature would score one point and thus be eligible for discontinuation of anticoagulation. We would be very wary of this practice. However, it should be noted that the physical findings of leg edema, erythema, and hyperpigmentation may signify abnormal venous return and residual thrombosis, and residual thrombosis has been associated with increased risk of VTE recurrence [57, 58]. So, whether the HERDOO2 score is used or not, these findings should be taken into account when determining anticoagulation duration.

The EINSTEIN CHOICE and AMPLIFY EXTEND trials [2, 3] appear to be making a major impact on duration of anticoagulation; both trials studied patients with provoked or unprovoked VTE who had been already treated for 6–12 months. The safety and efficacy results support strongly considering a decrease in the dose of rivaroxaban or apixaban to 10 mg once-daily and 2.5 mg twice daily, respectively, at the 6- to 12-month mark after risk benefit is reviewed. While follow-up data on VTE recurrence and bleeding was only obtained up to 12 months on the reduced dose regimens, the data offer the promise of protection from VTE recurrence with extended anticoagulation with a low bleeding risk [2, 3]. More data are needed in specific populations such as those with active cancer. In the HERDOO2 trial above, in low-risk women who discontinued anticoagulation, the recurrence rate was still 3.0% (95% CI, 1.8–4.8%) at 1 year – not necessarily a negligible number [55]. Perhaps risk-benefit would be favorable in such women placed on the EINSTEIN CHOICE or AMPLIFY EXTEND regimens. This has not been studied.

Overall, anticoagulation duration should be individualized and based upon an estimate of the risk of recurrence and bleeding. Some key points regarding anticoagulant duration are listed in Table 3. Please refer to the chapter specifically dedicated to anticoagulation selection and duration for more detail.

Table 3 Key points regarding duration of anticoagulation after acute VTE[a, b]

The risk of recurrent VTE and the risk of bleeding must be considered
The key issue determining anticoagulation is whether the VTE event was provoked or unprovoked, not whether a specific thrombophilia is present
VTE provoked by strong risk factors should be treated for 3 months
We consider extending anticoagulation to 6 months for an extensive clot burden in the legs and/or lungs, and symptoms that resolve more slowly
Continue anticoagulation in active cancer or for other persistent risk factors
Consider indefinite anticoagulation in unprovoked VTE
Young age and minimal provocation (e.g., long plane flight) may be enough to consider indefinite anticoagulation under some circumstances.
Factor V Leiden or prothrombin gene mutation heterozygosity alone is inadequate to proceed with indefinite anticoagulation
Patients with homozygosity for the latter thrombophilias, or with other inherited thrombophilias should be considered for indefinite therapy, but individualized
Acute VTE and APLAs (repeat + at 3 months) merits indefinite anticoagulation
Patients with persistent DVT by follow-up ultrasound should be considered for continued anticoagulation
Extending therapy beyond 6 months with half-dose rivaroxaban or apixaban may reduce the risk of recurrent VTE with a very low rate of major bleeding
For all but straightforward clinical decision making, expert consultation regarding these issues is advised

Abbreviations: *VTE* venous thromboembolism, *APLAs* antiphospholipid antibodies, *DVT* deep venous thrombosis

[a]These bullet points represent only a brief summary and are not meant be all inclusive

[b]These concepts generally apply to both acute DVT and PE

Thrombophilia Testing

While a range of thrombophilia studies are available and frequently ordered after acute PE, the utility of such testing is frequently debated [8, 12]. In the majority of acute VTE cases, there is little value of testing for thrombophilia, particularly after the first VTE or when is no family history of early VTE. As the NICE guidelines emphasize, testing should only be performed when it is likely to change the patient's management [59].

The patients who are least likely to benefit from such testing are those with major, transient provoking risk factors. Indeed, as part of the 2013 ABIM Choosing Wisely Campaign, the American Society of Hematology strongly advised against testing in such cases [60]. Similarly, in a patient with an active malignancy or known inflammatory or connective tissue disease, thrombophilia testing is unlikely to change management and is therefore unnecessary. Patients with autoimmune diseases such as thrombotic thrombocytopenic purpura, polyarteritis nodosa, polymyositis, and dermatomyositis, have a six-fold higher risk for the development of VTE. Despite this risk, routine serologic screening for such conditions is not recommended unless there is significant clinical suspicion of disease [61].

Despite the debate, thrombophilia testing after PE may be useful in some specific circumstances [8, 12]. Observational studies have reported an underlying hypercoagulable condition is identified in up to 40% of young patients with either a personal or family history of unprovoked VTE. Revealing a hereditary thrombophilia can have utility, with implications for family planning and may provide an explanation for prior miscarriages. The identification of a high-risk thrombophilia may raise awareness with regard to future high-risk settings for otherwise asymptomatic first-degree relatives. Knowledge of a prothrombotic condition may also prompt more intensive anticoagulation management or prophylaxis in a perioperative setting.

In some cases, awareness of a thrombophilia may indicate the need for specific changes in the anticoagulation regimen. A recent study compared warfarin to rivaroxaban for treatment of VTE in patients with high-risk, "triple-positive" APS (lupus anticoagulant, anticardiolipin, and β2-glycoprotein antibodies). The trial was terminated early due to excessive deaths, thromboembolic events, and major bleeding in the rivaroxaban group, so that warfarin is favored in these patients [62]. Thus, the presence of APS may result in a change in anticoagulation selection altogether. While warfarin appears to be the anticoagulant of choice for triple-positive VTE patients with APS, this does not imply that uncomplicated patients with APS who are not triple-positive and who have not had an arterial thrombotic event require warfarin over a DOAC. There is no evidence that patients with low-titer anticardiolipin or beta-2 glycoprotein antibodies require warfarin. Such patients should be individualized. APS testing should be considered in all young adults who have had one or more unprovoked venous or arterial thrombotic events. Testing should also be performed in VTE patients if there is a personal history of lupus or a first-degree family member with multiple early miscarriages. Indeed, several professional societies recommend testing for APS in patients who sustain an unprovoked PE or proximal DVT [24, 63, 64].

The timing and interpretation of thrombophilia testing depend on how recent the PE occurred and the type of anticoagulation prescribed. In most cases, there is little value of testing at the time the PE is diagnosed, as it is unlikely to result in a change in immediate management. Acute thrombus can also result in a transient decrease in protein C, protein S, and antithrombin levels, which may lead to misinterpretation and clinical confusion [12]. In patients treated with warfarin, checking protein C and S levels should also be delayed until after completion of therapy, as both are vitamin-K-dependent factors. Reference ranges should be adjusted for pregnant patients as well, as levels of protein C may slightly increase and protein S levels decrease during pregnancy. The second-trimester fall in free *protein* S *levels* is a physiologic *pregnancy* adaptation. Women who develop VTE during *pregnancy* should have *protein* S levels measured after the postpartum period to avoid misdiagnosis and treatment [12].

In patients on unfractionated heparin or LMWH, testing for lupus anticoagulant antibodies should be delayed at least 24–72 hours as most laboratories are unable to perform testing in the presence of heparin-based anticoagulation. Similarly, in patients anticoagulated with a DOAC, thrombophilia testing should be delayed for 48 hours (~5–6 half-lives) after therapy has been held. Testing for lupus

anticoagulant is best performed while off warfarin since it may cause false positives for this antibody. However, based on the TRAPS study [62], if there is high suspicion for APS at the time of VTE diagnosis, transition to warfarin rather than a DOAC should be a consideration until confirmation can be accomplished.

In summary, thrombophilia testing should be reserved for carefully selected patients with an unprovoked or recurrent PE with a strong family history of thrombosis or recurrent miscarriages. While a careful assessment of provoking factors should be outlined, an overall assessment of risk factors should be undertaken, a decision about thrombophilia testing made, and duration of anticoagulation determined.

Testing has a limited role in screening asymptomatic relatives of patients with known thrombophilia [65]. A meta-analysis of prospective cohort studies suggests that testing asymptomatic relatives is not helpful in low-risk thrombophilias, while the evidence in high-risk thrombophilias is unclear [31]. In such cases, discussion with a thrombosis expert is advised. Finally, in such settings, as with VTE patients, appropriate precautions include frequent standing and walking, as well as hydration during prolonged travel. All individuals, regardless of history or prior VTE, should understand that while the risk of acute VTE is very low after certain procedures such as knee arthroscopy, it can occur and subsequent frequent ambulation should be encouraged when possible. Key points regarding thrombophilia testing are outlined in Table 4.

Table 4 Key points regarding thrombophilia testing after acute PE[a, b]

No validated thrombophilia testing guidelines have been published
Recommendations for thrombophilia testing are not uniform
The majority of patients with VTE should not be tested for thrombophilia
Testing should be considered if it is likely to change management
VTE provoked by strong risk factors does not merit thrombophilia testing
Delay testing until after treatment for acute VTE event and off anticoagulation
Consider thrombophilia testing in certain unprovoked acute VTE cases
In particular, consider testing patients with first or subsequent unprovoked VTE before age 50 years and strong family history of VTE
Thrombosis in unusual locations such as splanchnic, hepatic or portal vein thrombosis merits consideration for JAK-2, paroxysmal nocturnal hemoglobinuria, and APLA testing
First-degree relatives are generally not tested – however, it is feasible that testing could impact on hormonal/oral contraceptive therapy[c]
For all but straightforward clinical decision-making, expert consultation regarding these issues is advised

Abbreviations: *PE* pulmonary embolism, *VTE* venous thromboembolism, *APLAs* antiphospholipid antibodies

[a]These bullet points represent only a brief summary and are not meant to be all inclusive

[b]These concepts generally apply to both acute DVT and PE

[c]Unprovoked VTE, for example, with positive thrombophilia testing, might result in modification of hormonal or contraceptive plans for a first-degree relative, even though negative testing in the unprovoked relative *should* lead to the same decision

Screening for Malignancy

The overall risk for VTE in cancer patients is four times greater than that of the general population; yet, the value of screening for occult malignancy in patients with an unprovoked PE has been a continuous topic of debate [66–70]. A systematic review published in 2008 analyzed 15 studies and concluded that previously undiagnosed cancer was frequent in patients with an unprovoked VTE [71]. The authors of this review postulated that a more extensive screening strategy may have better sensitivity in detecting underlying malignancy. A subsequent randomized controlled trial published by the same authors in 2015 tested this hypothesis [72]. A total of 850 patients were randomized after their first unprovoked VTE to undergo age-appropriate cancer screening with or without an additional CT scan of the abdomen and pelvis. The study found no statistically significant difference in the rate of occult malignancy identified between the two groups (3.2% of regular screening group, 4.5% of cases in the CT group). Furthermore, there was no difference in the average time to cancer diagnosis or cancer-related mortality after the first year. Currently, it is thus suggested that a thorough medical history and physical examination, basic blood work, chest radiograph, and age-specific and gender-specific testing according to national guidelines is an adequate occult cancer screening strategy for patients with unprovoked VTE [66]. For example, CEA, PSA, colonoscopy, and mammography should be strongly considered in appropriate individuals.

Other Aspects of Post-Pulmonary Embolism Management

Oxygen Requirement Post-PE

When oxygenation is a concern post discharge, the patient should be tested and placed on O_2. An O_2 requirement at rest or exercise is very unusual in patients in the weeks following discharge unless there is underlying CTEPH or other comorbid cardiopulmonary disease.

Inferior Vena Caval (IVC) Filters

Inferior vena cava filters fill a clear need in patients with acute VTE, particularly when anticoagulation is contraindicated, or fails to prevent acute PE. Major complications include insertion site bleeding or hematoma, filter migration, and penetration outside the vena cava. IVC filters should be considered for removal within the first 30–60 days after placement unless an indication persists [73].

Post-Thrombotic Syndrome (PTS)

While a detailed review of PTS is beyond our scope, persistent outpatient symptoms are common in patients with PE and or DVT. Persistent leg pain and swelling from residual DVT can be addressed with leg elevation, compressions stockings, and continued anticoagulation. While compression stockings have not been shown to reduce post-thrombotic syndrome based on the SOX trial [74], it is reasonable to consider well-fitted thigh-high stockings when pain and swelling persist. Those who experience particularly severe and extensive DVT should be considered for evaluation for compression syndromes such as May-Thurner, which may require ballooning and stenting, for example [75].

Post-PE Rehabilitation

Cardiopulmonary rehabilitation has been shown to be safe and effective shortly after acute PE. Patients who have had massive PE, extensive PE with severe RV dysfunction, cardiopulmonary comorbidities, or prolonged hospitalizations may benefit the most. In general, patients with extensive and symptomatic residual DVT should wait until symptoms improve before embarking on an aggressive exercise program. A large German cohort of PE patients underwent a 3-week inpatient rehabilitation program undergoing various forms of exercise training. Overall, this was shown to be safe but clear proof benefit was not demonstrated with certainty [76]. One small study of 19 patients found a three-month exercise and weight loss program after acute VTE resulted in better peak oxygen consumption compared to controls [77]. Furthermore, cardiopulmonary rehabilitation has been shown to improve exercise capacity and quality of life in patients with CTEPH who are not candidates for pulmonary endarterectomy [78].

Management of Recurrent VTE

Patients who experience recurrent VTE can be broadly categorized into two cohorts. The first are patients who experience another thrombotic event while on therapeutic anticoagulation, and the second group consists of patients who have recurrent VTE when anticoagulation was either discontinued or was subtherapeutic. Recurrent VTE is rare in compliant anticoagulated patients after acute PE, but can occur and is most common in the first month after initiation of therapy. There are no randomized trials or prospective cohort studies evaluating the management of recurrent VTE in patients on therapeutic anticoagulation. All guideline recommendations on this matter are weak recommendations based on low-level quality of evidence. In this group, the possibility may still be inadequate anticoagulation even though dosing appears to be therapeutic. This may be due to malabsorption,

inadequate dosing due to pharmacokinetics or drug–drug interactions, or poor medication compliance due to a myriad of biopsychosocial issues or financial constraints. When in the process of investigating the cause of a recurrent thrombosis in patients on therapeutic anticoagulation, the ACCP advises a switch to LMWH for at least 1 month [24]. LMWH dosing is weight-based and independent of diet or intestinal absorption, which ensures reliable anticoagulation while the cause of the recurrence can be determined. In patients who have recurrent VTE on therapeutic LMWH, the ACCP guidelines suggest increasing the dose of LMWH by one-quarter to one-third [24].

In patients who develop recurrent VTE despite adequate and appropriate anticoagulation, an evaluation for persistent ongoing prothrombotic stimuli is warranted. This may include inherited thrombotic disorders (protein C, S, or antithrombin deficiency), antiphospholipid syndrome, occult malignancy, or anatomic problems such as May–Thurner syndrome. Recurrent VTE while on therapeutic anticoagulation should prompt review of a potential underlying cancer [24]. Therapeutic options are limited in patients who have recurrent VTE when on appropriate therapy, and the efficacy of the DOACs in this patient population has not been studied. If appropriate and therapeutic anticoagulation has been confirmed, switching to LMWH or the addition of an IVC filter can be considered. Another possibility is misdiagnosis, as tumor or fat emboli may occasionally mimic thrombotic pulmonary embolism on a CT scan and would not be responsive to traditional anticoagulation therapy. Nearly all patients who experience a recurrent unprovoked VTE after completion of anticoagulation require indefinite anticoagulation and should be evaluated for underlying APS.

Post-PE Dyspnea

After acute PE, patients need to be followed for resolution of symptoms and for development of new ones. Recurrent PE, CTEPH, chronic thromboembolic disease (CTED), and other causes including deconditioning and comorbidities must be considered. The term “post-PE syndrome” is relatively new to the field of VTE and has generated interest [79, 80]. CTEPH is well defined and is discussed in detail in another chapter. CTED has been characterized as patients with residual pulmonary vascular obstruction but not meeting the resting hemodynamic criteria for CTEPH, yet still demonstrating symptoms and objective functional impairment with gas exchange abnormalities and/or with an exercise-induced rise in pulmonary artery pressure [81]. With exercise, there is an increased mean pulmonary artery pressure (PAP)/cardiac output slope, exaggerated rise in mean PAP to over 30–35 mm Hg, and no or inadequate fall in pulmonary vascular resistance [82]. Thus, CTED might be considered as an “incomplete” or milder form of CTEPH. Because both new and worsening dyspnea and persistent perfusion defects often develop after acute PE, the recognition of CTED can be challenging. Large CTEPH referral centers suggest that surgery may have benefit in amenable disease, with improved hemodynamics,

functional class, and exercise capacity [82, 83]. Based on the comorbidities and the complexities of the diagnostic workup, few data are available on the incidence or prevalence of CTED.

Imaging studies after acute PE indicates that incomplete resolution of the embolic burden is common. den Exter and colleagues [84] found that after 6 months of treatment, complete PE resolution had occurred in only 84.1% of the patients (95% confidence interval (CI): 77.4–89.4%) but that residual pulmonary vascular obstruction was not associated with an increase in recurrent PE. Sanchez, et al. [85] found that 73 of 254 patients (29%) had perfusion defects during follow-up (median 12 months) after acute PE, noting poorer outcome associated with persistent defects. Others have similarly found that residual obstruction is frequent [86, 87]. These persistent perfusion defects lead to increased alveolar dead space and ventilation-perfusion mismatching. The combination of these abnormalities in conjunction with persistent right ventricular dysfunction result in the dyspnea and deconditioning that occurs in CTEPH and CTED.

Patients either with or without residual pulmonary vascular obstruction (RPVO) may have persistent dyspnea after acute PE. Those patients with CTEPH or CTED are easy to comprehend. There is a third group of acute PE patients, with subsequent dyspnea and functional limitations and impaired quality of life without identifiable pulmonary vascular disease (normal lung perfusion scan) and persisting for longer than 3 months after initiation of therapy. There are also symptomatic patients *with* RPVO, generally mild, who do not fit CTEPH or CTED and thus also have "post-PE-related dyspnea [88]."

In the prospective ELOPE cohort of acute PE patients, excluding those with only subsegmental emboli and those with preexisting severe cardiopulmonary comorbidity, 46.5% of participants had a percent-predicted VO_2 peak of <80% at 1 year [89]. These patients had poorer performance on 6-minute walk testing and quality of life metrics compared to patients with a predicted VO2 peak of >80%. Some of these patients had residual pulmonary vascular obstruction. In this trial, it was noted that baseline or residual clot burden was not associated with the primary outcome. Thus, it is clear that patients with acute PE often have subsequent residual dyspnea, which may or may not be related to chronic RPVO.

CTEPH and CTED make physiologic sense, and both represent pulmonary vascular disease; it is this third group that requires better characterization. The term "post-PE syndrome" has been used by some to broadly encompass CTEPH, CTED, and this third group without proven vascular disease [90]. The two former diagnoses have stood on their own for many decades and might be best considered separately. There is no proof at present that a continuum exists beyond CTEPH and CTED, or that post-PE-related dyspnea is explained by microvascular residual pulmonary vascular disease. In spite of references that include all three groups of patients as "post-PE syndrome," at present, we use the term to refer to this more nebulous group of patients who remain symptomatic after acute PE with normal lung perfusion imaging; perhaps best termed "post-PE-related dyspnea" [88]. Pulmonary vascular obstruction, particularly milder forms may, however, not result in significant symptoms in all patients. We would thus also refer to patients *with*

evidence of residual pulmonary vascular obstruction by VQ scan, but who have a normal echocardiogram, no concomitant cardiopulmonary disease and CPET indicating deconditioning as "post-PE dyspnea." Cardiopulmonary exercise testing, echocardiography, right-heart catheterization, and VQ scanning are the key diagnostic modalities used to rule in CTEPH and CTED and to ascertain the degree in which deconditioning, coexisting cardiopulmonary disease, or other concomitant comorbid disease account for the post-PE dyspnea patients may experience. Perhaps future imaging modalities with increased sensitivity will identify residual, responsible pulmonary vascular defects, or rule them out unequivocally to help us better comprehend post-PE-related dyspnea, which does not meet criteria for CTEPH or CTED. Key points differentiating CTEPH, CTED, and post-PE dyspnea are outlined in Table 5. Post-PE diagnostic testing is discussed in a bit more detail below.

Table 5 Comorbidities associated with increased mortality after PE

	CTEPH	CTED	Post-PE dyspnea
Residual pulmonary vascular obstruction by imaging	Yes	Yes	Variable[a]
Resting PH	Yes	No[b]	No
Exercise-induced PH	Yes	Yes	No
Rest or exercise-induced hypoxemia	Variable	Variable	Variable
CPET consistent with PVD	Yes	Yes	No
Anticoagulation indicated	Yes	Yes	Variable[c]
Other therapy	PEA, BPA, medical therapy,[d] consider pulmonary rehabilitation	Possible PEA/ BPA, medical therapy,[d] consider pulmonary rehabilitation	Treat comorbidities, consider pulmonary rehabilitation

Abbreviations: *CTEPH* chronic thromboembolic pulmonary hypertension, *CTED* chronic thromboembolic disease, *PE* pulmonary embolism, *RVPO* residual pulmonary vascular obstruction, *PH* pulmonary hypertension, *CPET* cardiopulmonary exercise testing, *PVD* pulmonary vascular disease, *BPA* balloon pulmonary angioplasty, *RVPO* residual pulmonary vascular obstruction

[a]If imaging reveals no RPVO, or if there *is* RPVO and CPET and other parameters suggest no underlying pulmonary vascular disease, then post-PE dyspnea is likely due to deconditioning or comorbid disease

[b]Based on the 6th World Symposium on PH Proceedings (2018) definition, a pulmonary artery pressure of 21–24 mm Hg qualifies as PH. Thus, some might feel that CTED patients of this severity should fall under the category of CTEPH

[c]Here, anticoagulation only indicated if unprovoked PE or continued risk factors for PE are present, or if there is another non-PE indication for anticoagulation

[d]Pulmonary arterial hypertension medications are indicated in inoperable CTEPH, and possibly CTED (riociguat is the FDA-approved drug for CTEPH). The role of BPA is evolving. Also, cardiopulmonary rehabilitation should be considered in appropriate patients

Post-PE Diagnostic Imaging

Not until recently has there been wide acknowledgement of the complexity of post-PE care. Currently, the majority of published research on this topic consists of observational studies, and the only consensus statement for post-PE imaging is largely based on expert opinion [91]. Despite these limitations, there are principles of management that are nearly universally accepted. First and foremost, the timing and frequency of follow-up should be guided by the severity and trajectory of the patient's symptoms. We see the majority of patients within 2–3 weeks of discharge to guarantee appropriate therapy, compliance, and education with regard to symptoms that could signal recurrent DVT or PE during this period, which is high-risk for recurrence. We see patients again at the 3-month mark, and subsequent visits are generally every 3–6 months, depending on the clinical setting. We and others [88] do not believe that routine repeat imaging with transthoracic echocardiography (TTE), computed tomography, or exercise-testing is indicated if the patient is symptomatically improving, and ultimately symptoms resolve. While it has been suggested that persisting pulmonary vascular obstruction after acute PE may be associated with poorer outcomes [85–87], these patients are generally symptomatic and are thus identified and evaluated.

An assessment of symptoms in conjunction with a thoughtful physical exam is sufficient in most cases. However, we prefer to document normalization of the right ventricle in intermediate and high-risk patients. We recommend a six-minute walk test after the initial visit to establish an objective baseline for submaximal exercise tolerance, and this is repeated on subsequent visits in anyone with persisting symptoms of dyspnea. None of these tests have been shown to impact upon outcome in asymptomatic patients, and there is substantial variation among clinical practices.

As suggested above, more frequent visits are necessary in the patient with persistent dyspnea or diminished exercise capacity, and further testing is necessary. In the patient with persistent dyspnea, a resting TTE and lung imaging should be performed. Repeating these tests is usually reserved until after 3 months of therapeutic anticoagulation; however, earlier imaging may be warranted depending on the trajectory or severity of symptoms.

Several echocardiographic variables have been suggested to predict long-term functional impairment; however, comparing to prior cardiac imaging has the greatest utility. Worsening in right ventricular parameters require further investigation for with lung imaging and potentially right heart catheterization. Repeat CT angiography can be useful in the setting of a prior study, although chronic PE can be more challenging to detect radiographically. A normal VQ scan guarantees that CTEPH is not present and would appear to rule out that RPVO is contributing to symptoms.

In patients who report primarily exertional symptoms, the TTE may not be adequately sensitive to detect an abnormality. Repeating the six-minute walk test is a simple means by which to objectively assess submaximal exercise capacity and screen for exercise-induced hypoxemia but does not provide useful diagnostic information. While there are no definitive data on the use of functional tests in

PE follow-up, a formal noninvasive CPET with bicycle ergometer or treadmill is often required as it can assess the severity of disease, prognosis, and response to therapy in patients with pulmonary hypertension [57]. Furthermore, a maximal CPET can often reveal whether exercise limitation is primarily cardiac, pulmonary, or metabolic in etiology. In such cases, the clinician can focus attention to the limiting variable, which not infrequently is due to confounding comorbid conditions.

While the clinician is tasked with making complex diagnostic and therapeutic decisions during post-PE care, the clinic itself in which follow-up occurs must also be appropriately trained and equipped to facilitate an organized, patient-centered visit. This includes trained nursing and clinical support staff who can obtain accurate vitals including orthostatics when needed, measure pulse oximetry, conduct six-minute walk tests, and administer supplemental oxygen if necessary. An integrated pathway should be in place to obtain labs and arrange for follow-up imaging in a time-efficient manner that minimizes hurdles for the patient. Given the complexities of post-PE management, the ANMCO position paper on this topic suggests follow-up to be conducted in a multidisciplinary clinic that mirrors similar clinics for other complicated medical conditions (congestive heart failure, solid organ transplantation, etc.) [91]. This allows the patient to be evaluated and obtain all necessary testing at one site on one visit. Our belief is that if PE experts who are facile with all aspects of the disease are present, then a multidisciplinary clinic is unnecessary, otherwise it is suggested.

Long-Term Survival and VTE Recurrence: What to Tell the Patient

Accurate patient-specific predictions of long-term mortality after PE have been difficult to estimate due to the heterogeneity of the PE population and the scope of the disease. A high percentage of patients who die from acute PE die before they reach the hospital while those surviving to discharge have a very low mortality due to recurrent PE. One large clinical trial enrolling patients with intermediate-high risk PE (abnormal right ventricle by echocardiography and abnormal troponin) showed a mortality at 7 days of only 1.2% (thrombolysis + anticoagulation group) and 1.8% (placebo + anticoagulation group) [92]. This suggests that once patients reach medical care, mortality is low. It should be realized, however, that there is inherent bias in patient selection for clinical trials with exclusions for certain comorbidities, clot burden, clinical stability, or bleeding risk. Still, the subsequent mortality rate from PE for patients surviving to hospitalization and subsequently to discharge is very low.

Once a patient survives the initial event and is discharged, morbidity and mortality are often determined by comorbidities. Indeed, death after PE is most often attributable to complications of comorbid conditions and not the embolism itself

Table 6 Comorbidities associated with increased mortality after PE

Registry/trial	Study size	Comorbidities with increased mortality
PIOPED [93] 1985–6	399 patients, prospective, 6 centers, United States	Age > 60, cancer, CHF, chronic lung disease
ICOPER [94] 1995–6	2454 patients, prospective, 52 centers, 5 countries	Age > 70, cancer, CHF, COPD
RIETE [95] 2001 to present	41,017 patients, prospective, 170 centers, mostly Spain	Advanced cancer, chronic kidney disease, immobilization
Ng AC, et al. [96] 2000–7	1023, retrospective, single center, Australia	Cancer, sepsis, acute MI, CHF, stroke
Klok FA, et al. [97] 2001–7	866 patients, retrospective, 2 centers, Netherlands	Cancer, recurrent PE, cardiovascular disease
IPER [98] 2006–10	1716 patients, prospective, 49 centers, Italy	Advanced age, cancer, low BMI
FOCUS [99] 2016–17	1000 patients, prospective, Germany	Ongoing, 2-year follow-up

Abbreviations: *PE* pulmonary embolism, *CHF* congestive heart failure, *COPD* chronic obstructive pulmonary disease, *MI* myocardial infarction, *BMI* body mass index

[93–96]. Future morbidity and mortality due specifically to VTE, however, is based primarily on recurrent PE (and thus, persisting risk factors for acute VTE) and CTEPH. Specific comorbidities have been consistently shown to be associated with an increased mortality following acute PE (Table 6) [93–96]. Therefore, it is imperative to closely review the past medical history and optimize high-risk comorbidities in coordination with the primary care provider and other involved specialists.

Conclusions

A number of issues must be addressed during follow-up after acute PE, most importantly, duration of anticoagulation and determination of resolution of symptoms. Unresolved symptoms, primarily dyspnea on exertion, must be explored, and if present, CTEPH or chronic thromboembolic disease without PH must be ruled out. Symptoms due to these entities or related to prior PE must be differentiated from other comorbidities such as underlying heart failure, chronic lung disease, anemia, and deconditioning. Research is evolving and building on trials like EINSTEIN CHOICE and AMPLIFY EXTEND will give us more insight into duration and intensity of therapy. Consistent and closer follow-up of acute PE patients in patients focused on this disease may be of great assistance in identifying CTEPH rather than relying on the delayed referral once CTEPH has fully evolved. Future studies will offer more information on the impact of persistent residual vascular obstruction in patients without CTEPH but who continue to have symptoms.

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Epidemiology and Diagnosis of Chronic Thromboembolic Pulmonary Hypertension

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Background

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease defined by the presence of pulmonary hypertension (PH) due to a combination of thrombo-fibrotic occlusion of major pulmonary arteries and a concomitant microscopic vasculopathy [1]. CTEPH is currently classified as group 4 pulmonary hypertension [2], and it is the only form of pulmonary hypertension that can be treated quite effectively with interventional procedures, particularly, a surgical intervention called pulmonary endarterectomy (PEA), also known as pulmonary thromboendarterectomy (PTE).

Although some debate still exists [3], it is generally accepted that one or more episodes of pulmonary embolism (PE) trigger the development of CTEPH [4]. The transition from acute to chronic PE is poorly understood. Impaired fibrinolysis, abnormal remodeling of the emboli with impaired angiogenesis, and inflammation are postulated as pathogenic mechanisms [5]. Chronic PE lesions, by virtue of their fibrotic nature, narrow large pulmonary arteries. In nonobstructed arteries, a high-flow high-pressure state ensues, which leads to endothelial and smooth muscle cell dysfunction and proliferation, which is the cause of the microscopic vasculopathy [1]. The

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combination of large vessel obstruction and microscopic vasculopathy accounts for pulmonary pressure elevation and consequently right ventricular dysfunction.

In this chapter, we will review the epidemiology of CTEPH, including risk factors and screening strategies, and we will describe the extensive evaluation needed to make a proper diagnosis of CTEPH.

Epidemiology of CTEPH

The exact prevalence and incidence of CTEPH are not known. CTEPH is a rare disease, yet underdiagnosed at the same time, which makes defining its epidemiology challenging. A diagnostic delay of 14 months has been documented in a multicenter CTEPH registry [6]. CTEPH presents with nonspecific symptoms and signs, and is frequently mistaken for other more common conditions such as recurrent thromboembolic events or obesity [7]. Physicians frequently fail to utilize the guideline-recommended tests for the diagnosis of CTEPH [8]. CTEPH patients typically see multiple healthcare providers from different disciplines before arriving at the correct diagnosis [9]. Nonetheless, registry data and several observational studies allow for some estimated CTEPH epidemiology. Registry data from the United Kingdom suggest that CTEPH prevalence ranges from 10.8 to 38.4 cases per million inhabitants [10]. CTEPH accounts for 18–25% of cases in pulmonary hypertension registries [11]. Regarding CTEPH incidence, estimates range from 0.9 up to 5.7 cases per million inhabitants per year [12, 13]. The incidence of CTEPH after acute PE is a matter of much debate.

There is a great deal of variability in the reported incidence, ranging from 0.1% to 9.1% [14]. The reasons for this variability in CTEPH incidence include major differences in the selection of the studied patient populations and variability in how CTEPH is defined, as some studies did not use right heart catheterization (RHC) to diagnose CTEPH. A meta-analysis that included 16 low-bias prospective studies that used right heart catheterization to diagnose CTEPH, after a mean follow-up of approximately 2 years, arrived at a pooled incidence of 0.56%, in all comers with PE. When including only survivors with PE, the incidence was 3.21% and when including survivors without major comorbidities, the pooled incidence was 2.78% [15]. The included studies had incidence rates that ranged from 0.46% to 6.2%. Incidence tended to be higher in survivors and survivors without comorbidities, the populations where screening for CTEPH might make the most sense. However, a recent multicenter prospective study conducted in Switzerland that enrolled a population of survivors without major comorbidities showed an incidence rate of 0.79% over 2 years [16]. One potential explanation is that in some studies, the acute PE index event may in fact be already the initial presentation of CTEPH. This was demonstrated by a prospective study by Guerin and coworkers of 146 PE patients followed up for a median of 26 months. They found seven cases of CTEPH for an incidence of 4.8%. The authors then reviewed all the CT scans images and

echocardiograms of these seven patients from the index PE event. They found that every case had at least two CT signs of chronic PE, and that five cases (71%) had an echocardiographic estimated of systolic pulmonary artery pressure >60 mmHg [17]. These findings strongly suggest that at least five of the seven cases already had CTEPH at the time of what was believed to be the acute PE presentation, for a true incidence of CTEPH of 1.4%. This study demonstrated that CTEPH patients can have an "acute" presentation. More accurately, these are cases mistaken for acute PE with right ventricular strain, while being CTEPH all along. Figure 1 shows a summary of all prospective studies that used right heart catheterization to diagnose CTEPH. At the moment, the exact incidence of CTEPH following a PE remains uncertain, but a sensible estimate is probably between 1% and 2% within the next 2 years after a PE [18].

As the venous thromboembolic disease is extremely prevalent, even with this low incidence rate, the disease burden is significant. This is further compounded by the fact that many patients with CTEPH do not have a previous history of PE. In the international (Europe and Canada) multicenter CTEPH registry, only 75% of patients had a documented history of acute pulmonary embolism [6]. In Japan, only 15–33% of CTEPH patients report a history of PE [19]. Finally, there is a larger universe of survivors of PE who, within the next 2 years, have persistent or worsening symptoms of reduced functional status and measurable limitations of cardiopulmonary function on exercise testing, the so-called post-PE syndrome [20]. When these patients also have chronic thromboembolic lesions in the pulmonary vasculature evident on imaging studies, without resting pulmonary hypertension, this constitutes symptomatic chronic thromboembolic disease (CTED). Even less is known

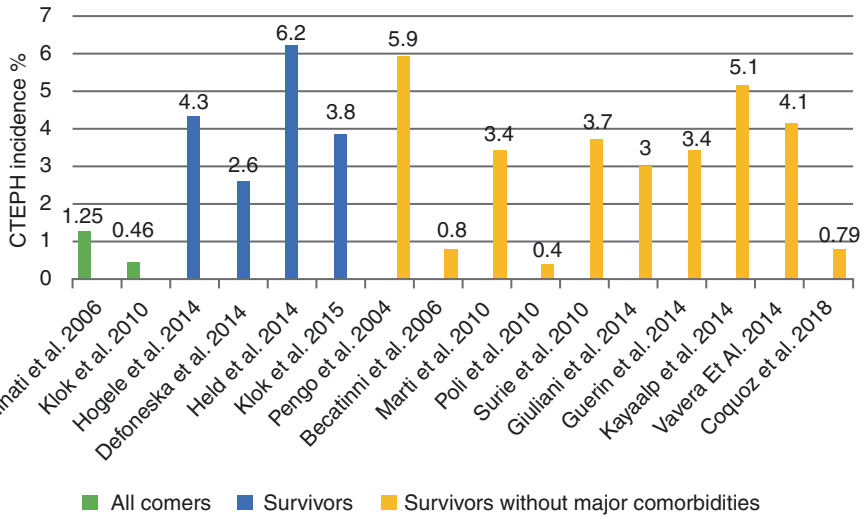

Fig. 1 CTEPH incidence rates following pulmonary embolism (PE) in prospective studies that used right heart catheterization to confirm the diagnosis of CTEPH [17, 36, 65–76]

about the prevalence and incidence of these relatively novel entities [11].

Risk Factors for CTEPH

The risk factors for CTEPH are multifactorial and even outside of the insult due to an acute pulmonary embolism. This may be attributed to the complex pathobiology of CTEPH which constitutes a makeup of genetic variability underlying inflammatory states, preexisting autoimmune disease, and prothrombotic states.

When compared to patients with pulmonary arterial hypertension (PAH), risk factors for CTEPH include a previous venous thromboembolism (VTE) event, recurrent VTE, elevated levels of factor VIII, non-O blood groups, patients who have had a splenectomy, ventricular atrial (VA) shunts, infected pacemaker leads, chronic inflammatory conditions such as inflammatory bowel disease, antiphospholipid syndrome, history of cancer, and thyroid replacement therapy [21–23]. These data have prompted PE guidelines to recommend considering these conditions as predisposing to CTEPH in patients with acute PE [24]. However, it is important to note that these studies included patients with an already confirmed diagnosis of CTEPH and looked at risk factors for CTEPH compared to patients with PAH. It is unclear if these risk factors can be extrapolated to a population of survivors of acute PE. In prospective studies of patients followed after an acute PE, recurrent PE and unprovoked PE were found to be major risk factors for the development of CTEPH, with odds ratios of 3.16 and 4.13, respectively [15]. In the most recent prospective follow-up of acute PE patients, the only underlying condition associated with CTEPH was the presence of antiphospholipid antibodies (APS) [16].

Screening for CTEPH

CTEPH is a rare disease that can complicate a very common condition such as VTE, and that requires a cumbersome evaluation and expertise to diagnose. At the same time, CTEPH is under-recognized and undertreated, even though very effective, even curative therapies exist. As such, there is a strong desire to screen CTEPH following a PE, yet studies to support screening are scarce and limited. Further complicating this matter, dyspnea or function limitation is very common after a PE. Around 36% of patients report dyspnea over 2−3 years after PE [25, 26] and 46.5% have a reduced peak VO_2 after 1 year [27]. However, dyspnea after PE is actually rarely related to the previous PE itself, and most commonly explained by the underlying patient's comorbidities such as obstructive lung disease, systolic and diastolic left heart failure, and obesity [25]. Follow-up imaging frequently shows persistent perfusion defects. Studies using CT scans, approximately 6 months after the initial PE, demonstrate persistent perfusion defects in 15–25% of patients [28–30]. Using the perfusion lung scan after 6–12 months, the rate of perfusion defects has ranged from 28% to 52% [28, 31–34]. However, the presence of perfusion defects does not necessarily correlate with low functional capacity, as demonstrated in the Evaluation of Long-Term Outcomes After PE (ELOPE) study [27]. Yet, residual perfusion vascular obstruction 6 months after PE is associated with an increased risk of recurrent VTE and CTEPH [34]. Finally,

as discussed in the previous section, it is not clear how to identify a "high risk" population of PE patients that is more likely to develop CTEPH, with the strongest risk factors being unprovoked PE, recurrent PE, and anti-phospholipid antibodies.

To address this question, Klok et al. derived and validated a CTEPH rule-out criteria demonstrating a sensitivity of 100% for the detection of CTEPH in a cohort of 134 patients followed for 6 months after PE with a CTEPH incidence of 4.5% [35, 36]. The two ruled-out criteria were electrocardiographic findings of right ventricular strain and elevated natriuretic peptide levels. In another study by the same group, they performed a post-hoc patient-level analysis of three observational studies including 772 patients without end-stage cancer or cardiopulmonary disease. Six months after PE, if an echocardiogram was suggestive of pulmonary hypertension, patients underwent chest imaging and right heart catheterization. CTEPH incidence was 2.8%. Independent predictors of CTEPH were unprovoked PE, hypothyroidism, symptoms lasting more than 2 weeks, and right ventricle (RV) dysfunction during the acute PE. Diabetes and thrombolysis or embolectomy were associated with a lower risk of CTEPH. These were combined into a prediction score shown in Table 1. A score of six or less (low score) had a sensitivity of 91%. The CTEPH incidence in low-risk patients was 0.38%, while it was 10% in those with a high score. This is the first published CTEPH prediction score and represents an advancement in our understanding of how to screen for CTEPH. However, it is surprising to see diabetes and thrombolysis/embolectomy as "protective" to CTEPH, and they are likely to be just anomalies of the statistical testing and the nature of the study design and population. It is worth noting that insulin resistance is associated with pulmonary hypertension and PE, and that thrombolysis did not prevent CTEPH over long-term follow-up in patients enrolled in the randomized placebo-controlled Pulmonary Embolism International Thrombolysis (PEITHO) trial [26]. Based on these data, the investigators designed the InShape II study (Clinical Trial NCT02555137) for the early detection of CTEPH. This is a prospective study of PE patients who at 3–6 months will be evaluated first with the CTEPH prediction score and symptoms, then with the rule-out criteria, followed by echocardiography and ventilation–perfusion (VQ) scan, and RHC when the echo probability of PH is intermediate or high. At the moment of this writing, the study has completed enrollment of 424 patients, but follow-up is ongoing.

Table 1 Prediction score for CTEPH after Acute PE

	Points	Performance ≤ 6
Unprovoked PE	+6	Sensitivity: 91%
Known hypothyroidism	+3	
Symptoms > 2 weeks before PE diagnosis	+3	Specificity: 75%
RV dysfunction on CT or Echo	+2	Positive predictive value: 10%
Known diabetes mellitus	−3	
Thrombolysis/embolectomy	−3	Negative predictive value: 99.6%

Adapted from Klok FA, et al. *J. Thromb Haemost* 2016
Abbreviations: *PE* pulmonary embolism, *RV* right ventricle, *CT* computerized tomography

The INPUT study has tested a different strategy to screen for CTEPH. This is a prospective multicenter Swiss study that screened patients 6, 12, and 24 months after PE by first asking for dyspnea via a phone survey and then performing an echocardiogram for those with new or unexplained dyspnea, followed by RHC and imaging tests to diagnose CTEPH in patients with possible pulmonary hypertension by echocardiography [16]. The authors analyzed 508 patients excluding those with severe comorbidities. The 2-year incidence of CTEPH was 0.79%. Echocardiograms were needed in 20–23% of the study population. The algorithm had a senility of 100% and a specificity of 81.6% for the detection of CTEPH. Importantly, no additional cases of CTEPH were found by cross-referencing the Swiss Pulmonary Hypertension Registry. Also, all the acute PE CTs were reviewed, and none had evidence of underlying CTEPH at the time. The only baseline condition associated with an increased risk of CTEPH was the presence of anti-phospholipid antibodies.

Another study that will provide additional information is the Follow-Up after acute pulmonary embolism (FOCUS) study [37]. This is a prospective multicenter German study where 1000 "all comers" will be followed up for 2 years (until August 2020). At 3, 12, and 24 months after the PE, patients will be evaluated with the New York Heart Association (NYHA) class, 6-minute walk test, echocardiography, biomarkers, and quality of life and exercise testing. This study attempts to define not only the incidence of CTEPH, but also the incidence of the post-PE syndrome.

The most recent PE guidelines from the European Society of Cardiology in conjunction with the European Respiratory Society recommend routine clinical evaluation 3–6 months after acute PE (level I recommendation) (Fig. 2) [24]. While this certainly represents a step forward to improve the recognition of CTEPH, several questions remain. As stated above, several so-called "risk factors" for CTEH are not really well validated in an acute PE population. Unprovoked PE, recurred PE, and echo evidence of RV dysfunction and pulmonary hypertension at the time of the acute PE, and the antiphospholipid antibody syndrome (APS) are the most consistent risk factors. The above-discussed studies and the recent guidelines do not address patients who have RV dysfunction and PH on echo during the acute PE presentation. We recommend that those patients have an echo repeated after 6–12 weeks to ensure RV recovery and to make sure that this was not an "acute" presentation of CTEPH. Finally, exercise testing and perfusion lung scanning need to be considered in symptomatic patients with otherwise unexplained dyspnea even with a normal echo, as symptomatic CTED is increasingly being recognized. Routine screening is not recommended in survivors of pulmonary embolism who are on anticoagulation and are asymptomatic, 3 months following the acute event.

Diagnosis of CTEPH

CTEPH should be suspected in three groups of patients: (i) anyone with pulmonary hypertension; (ii) anyone with cardio-pulmonary symptoms that persist or worsen following an acute pulmonary embolism; and (iii) anyone with

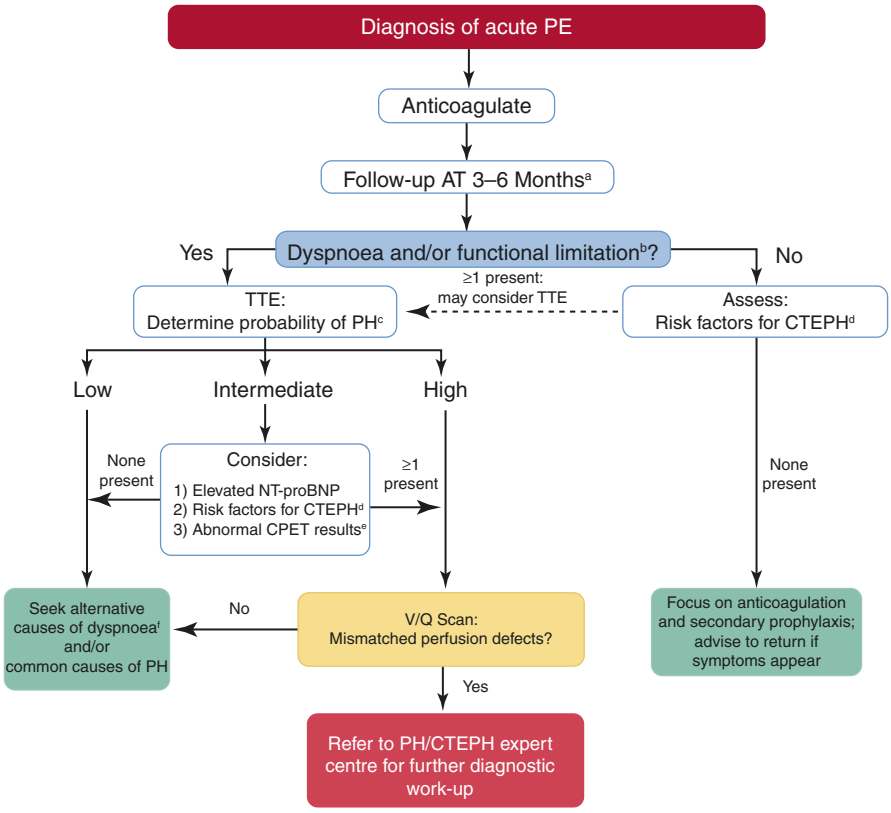

Fig. 2 Follow-up strategy and diagnostic workup for long-term sequelae of PE recommended by the 2019 ESC PE guidelines

unexplained dyspnea. In these three populations of patients, the initial steps to screen for CTEPH include a transthoracic echocardiography to assess for pulmonary hypertension and RV function, and a ventilation–perfusion (VQ) scan to look for mismatched perfusion defects. The diagnosis of CTEPH is confirmed by performing some form of pulmonary angiography (via computed tomography, digital subtraction angiography (DSA), and/or magnetic resonance imaging) to assess the extent and location of the chronic thromboembolic lesions, and a right heart catheterization to establish the presence, pattern, and severity of pulmonary hypertension. Ultimately, the diagnosis of CTEPH is based on the detection of pulmonary hypertension caused by chronic thromboembolic pulmonary vascular obstruction.

Of note, the entity known as a symptomatic chronic thromboembolic disease (CTED) is characterized by similar symptoms and imaging findings to CTEPH but without pulmonary hypertension at rest. Patients with CTED are symptomatic due to an abnormal pulmonary hypertensive response to exertion and/or inefficient gas exchange due to increased dead space ventilation. The diagnosis is challenging and

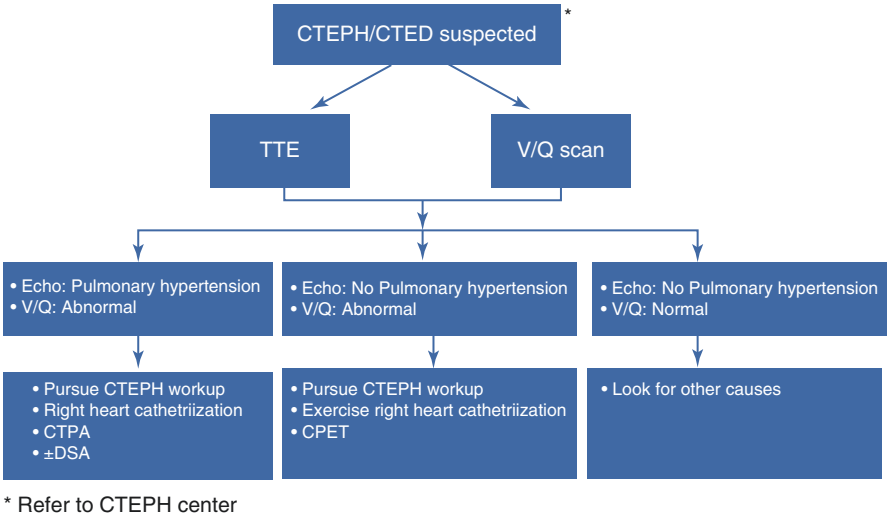

Fig. 3 CTEPH diagnostic algorithm. Abbreviations: CTED chronic thromboembolic pulmonary vascular disease, CTEPH chronic thromboembolic pulmonary hypertension, TTE transthoracic echocardiogram, PH pulmonary hypertension, CPET cardiopulmonary exercise testing, VQ ventilation perfusion scintigraphy

requires exercise testing [RHC and/or cardiopulmonary exercise testing (CPET)] to establish causality between the chronic thromboembolic vascular obstruction and the patient's symptoms. Further details are beyond the scope of this chapter.

Figure 3 depicts our proposed diagnostic algorithm for suspected CTEPH. In the following sections, we have discussed in detail the clinical presentation and diagnostic studies.

Symptoms and Exam

Exertional dyspnea is usually the characteristic symptom of patients with CTEPH. These patients see a progressive decline in their exercise capacity and ultimately experience dyspnea at rest. As the disease worsens and right heart dysfunction ensues, symptoms such as peripheral edema, pre-syncope, exertional chest pain, and syncope become more pronounced. Hemoptysis due to engorged collateral circulation is sometimes observed. As these symptoms are fairly nonspecific, it is no surprise that there is often a delay in diagnosing patients with CTEPH. A "honeymoon" period of months to years since the initial PE before symptoms of CTEPH appear is common. In many patients, especially those without a history of previous PE or deep vein thrombosis (DVT), the presentation may be clinically indistinguishable from other forms of severe PH [38]. Findings on physical exam are also nonspecific and include a more pronounced pulmonic component of the second heart sound. As the disease progresses and there is a progression to right-sided heart failure,

findings such as a murmur associated with tricuspid regurgitation, right ventricular heave, jugular venous distention, peripheral edema, ascites, and hepatomegaly may be noted. Some patients with CTEPH also exhibit the presence of a high-pitched blowing flow murmur best heard over the lung fields. Unique to CTEPH, this is thought to be due to turbulent blood flow through narrowed and partially obstructed proximal pulmonary arteries and is seen in about 30% of patients [39].

EKG

Electrocardiogram (EKG) can show signs of right ventricular hypertrophy, ischemic changes with inversions of the T waves, right bundle branch blocks, and other indicators of right heart strain. Interestingly, it has been shown that CTEPH can be ruled out if an EKG fails to show signs of right ventricular hypertrophy and if the N-terminal pro-brain natriuretic peptide (NT-proBNP) is within normal limits [40]. This underscores the useful information that simple modalities such as the EKG continue to provide in the imaging era.

Chest X-Ray

Chest radiographs are of limited value in the early detection of CTEPH. CTEPH may result in right atrial and ventricular enlargement on the radiograph. More specific findings include asymmetric enlargement of the central pulmonary arteries (which suggests an abnormality within the proximal vascular bed) and evidence of scar-like lesions or multifocal atelectatic bands in the periphery of the lung parenchyma.

Pulmonary Functions Tests

Spirometry is often normal in patients with CTEPH. Most patients do exhibit a mild reduction in the diffusing capacity for carbon monoxide (DLCO) [41].

Echocardiography

Echocardiography is a frequently used modality in patients with suspected CTEPH as an initial screening test. It allows for useful noninvasive assessment of right ventricular function and size, severity of tricuspid regurgitation, systolic pulmonary arterial pressure, and right atrial pressure. Usual findings in patients with CTEPH include right ventricular hypertrophy, depressed right ventricular systolic function, flattening of the interventricular septum throughout the cardiac cycle,

dilation of the inferior vena cava to more than 2 cm, and a small underfilled left ventricle. Echocardiography may miss pulmonary hypertension in 10−31% of cases and may particularly miss these findings in the early stages of the disease process [42].

Ventilation/Perfusion Scintigraphy (VQ)

VQ scanning is a highly sensitive screening test for CTEPH. A normal scan effectively excludes CTEPH and has a sensitivity of 90–100% and a specificity of 94–100% [43, 44]. Its advantages include the binary result in terms of being abnormal or normal hence allowing for easy interpretation (Fig. 5), limited radiation dose, no need for intravenous contrast agents, and excellent sensitivity. It is the imaging procedure of choice in patients presenting for workup of CTEPH. VQ scanning typically shows one or more segmental or larger mismatched ventilation–perfusion defects. In contrast, patients with group 1 pulmonary arterial hypertension typically exhibit a normal perfusion scan or one characterized by subsegmental defects. While CT pulmonary angiography (CTPA) technology continues to improve and more recent studies suggest improving sensitivity, VQ scanning remains the preferred initial test in the workup of CTEPH due to its ease of interpretation. VQ scans may be imperfect in assessing the burden of vascular obstruction in settings where recanalization of the pulmonary arteries has taken place following the embolic event; in these settings, the radioisotope agent can reach the periphery of the lung being highlighted as normally or hypoperfused areas. This may be one of the reasons why perfusion abnormalities on VQ scan can sometimes underestimate the extent of thromboembolic disease observed on angiography [45]. Abnormal perfusion defects can also be seen in other disease processes such as pulmonary-veno-occlusive disease, fibrosing mediastinitis, large vessel vasculitis, pulmonary artery sarcoma, radiation therapy, and extrinsic vascular compression due to malignancy.

Single Photon Emission Computed Tomography (SPECT-VQ)

While VQ scanning continues to be the initial screening test of choice, it is not free from limitations. Due to the two-dimensional nature of the imaging technique, lung segment overlap and shine-through can cause errors in the localization and quantification of perfusion defect. Additionally, as discussed above, an abnormal VQ scan is not diagnostic of pulmonary thromboembolic disease, and several other differential considerations can mimic the appearance. To overcome these limitations, SPECT VQ scans have been put forth as an alternative. Several studies have shown that SPECT imaging provides advantages over conventional planar imaging and lessens the number of nondiagnostic scans [46–48]. Using a low-dose noncontrast CT for attenuation correction, a SPECT-CT VQ imaging is also possible. While this increases the radiation dose by a minor amount, the anatomic CT images can be used to rule out

false-positive cases of VQ scans such as pneumonia and neoplasm, thereby increasing the specificity. Several studies and few meta-analyses have shown improved specificity and overall accuracy with SPECT-CT VQ scanning compared with conventional and SPECT VQ scanning [49, 50]. However, data on these newer modalities are still limited and larger studies are needed for conclusive implementation in routine practice. Also, data on inter-modality comparison of perfusion information need to be compared carefully and more experience and validation data are the need of the hour [51].

Computed Tomography Pulmonary Angiography (CTPA)

Once CTEPH is suggested on the basis of VQ scanning, CTPA is usually required as an additional study. It serves the purpose of differentiating CTEPH from other competing diagnoses and also is used to assess operability in patients. It allows for a comprehensive assessment of the pulmonary vasculature, lung parenchyma, mediastinum, and the collateral circulation. CTPA has a high diagnostic accuracy for the assessment of chronic thromboembolic lesions in the main, lobar, and segmental pulmonary artery levels (Table 2). Abnormalities that can be seen in patients with CTEPH include dilation of the main pulmonary artery (patients with CTEPH often have asymmetric enlargement of the proximal pulmonary artery), right ventricular enlargement, complete or partial obstruction of the pulmonary arteries, eccentric wall adherent thrombi with calcifications (as opposed to the central filling defect in acute PE), organized bands, webs, areas of post-stenotic dilatation, mosaic attenuation of the lung parenchyma, subpleural wedge-shaped opacities and scars denoting pulmonary infarcts, and enlargement of bronchial arteries and neighboring vessels resulting in increased bronchopulmonary collateral flow (this helps distinguish CTEPH from group 1 PAH, where this collateralizing occurs in less than 1% of patients).

CTPA can also be used to differentiate acute thromboembolic events versus chronic pulmonary embolism. In an acute event, in the case of total occlusion of the vessel, the vessel expands secondary to pulsatile flow, whereas in chronic disease, the vessel distal to the obstruction is markedly attenuated. In the case of partially obstructed vessels, an acute clot usually results in acute angles within the vessel lumen, whereas CTED results in the formation of obtuse angles, with the vessel

Table 2 Diagnostic performance of pulmonary angiography techniques

	Sensitivity		Specificity	
	Main/lobar	Segmental	Main/lobar	Segmental
CTPA	100%	100%	100%	99.3%
MRA	83.1%	87.7%	98.6%	98.1%
DSA	65.7%	75.8%	100%	100%

Adapted from Ley S et al. Eur Radiol 2012

Abbreviations: *CTPA* computed tomography pulmonary angiography, *MRA* magnetic resonance angiography, *DSA* digital subtraction angiography

lumen along with several areas of webs and bands. CTED may also show areas of mosaic attenuation of the lung parenchyma and fibrotic bands which may represent resolved infarcts [52].

Importantly, a "negative" read of a CTPA frequently does not exclude CTEPH (Fig. 4). This is due to the fact that the recognition of chronic thromboembolic lesions on CTPA, particularly at the segmental and more distal level, requires considerable experience and expertise that are not universally available. This is a main reason why guidelines continue to recommend the VQ scan as the screening test of choice for CTEPH in spite of recent studies, from expert centers, showing that CTPA also has excellent sensitivity [53].

Dual-Energy CT

Dual-energy CT (DECT) has emerged as an important new technique in the evaluation of CTEPH. Exploiting the differences in attenuation of materials with higher atomic weights such as iodine, material decomposition images can be generated. For the purpose of pulmonary vascular imaging, this entails the mapping of iodine within a voxel of lung tissue called perfused blood volume (PBV) images. Studies have shown that vascular information of the lung parenchyma obtained from the PBV images serves as a good surrogate marker of perfusion.

With the ability to provide anatomic and functional information on a single test, DECT can emerge as a one-stop-shop imaging technique for evaluation of CTEPH. With the addition of perfusion maps, the diagnostic accuracy of CT is improved [54]. Also, studies have shown that PBV maps can be helpful in differentiating between acute and chronic PE. Using delayed imaging, it has been shown that lungs affected by chronic PE can show delayed enhancement due to the presence of collaterals. Also, limited studies have shown moderate-to-good correlation between the perfusion maps and VQ scanning [55]. Beyond diagnosis, DECT offers promise in the hemodynamic assessment. In one study on 46 patients, lung PBV score was significantly correlated with the pulmonary artery pressure (PAP; mean, rho = 0.48; systolic, rho = 0.47; diastolic, rho = 0.39), pulmonary vascular resistance (PVR; rho = 0.47), and right ventricular pressure (RVP; rho = 0.48) (all p values <0.01) [56]. DECT-based PBV maps also allow calculation of various vascular indices that can reflect the state of the underlying vascular bed, and indirect evidence of small vessel vasculopathy [57]. PBV maps also allow for preoperative planning and for the assessment of response to therapy. With increasing utilization of balloon pulmonary angioplasty (BPA), PBV maps offer the potential to identify good targets for BPA and also assess for the success of the therapy [58].

While the advantages of DECT are many, the limitations of the study also need to be kept in mind. Streak artifacts related to contrast might hamper the assessment of perfusion defects. Similarly, underlying parenchymal lung disease such as emphysema and honeycombing might cause false-positive perfusion defects. Similarly, extensive small airway disease can demonstrate areas of perfusion abnormalities as well.

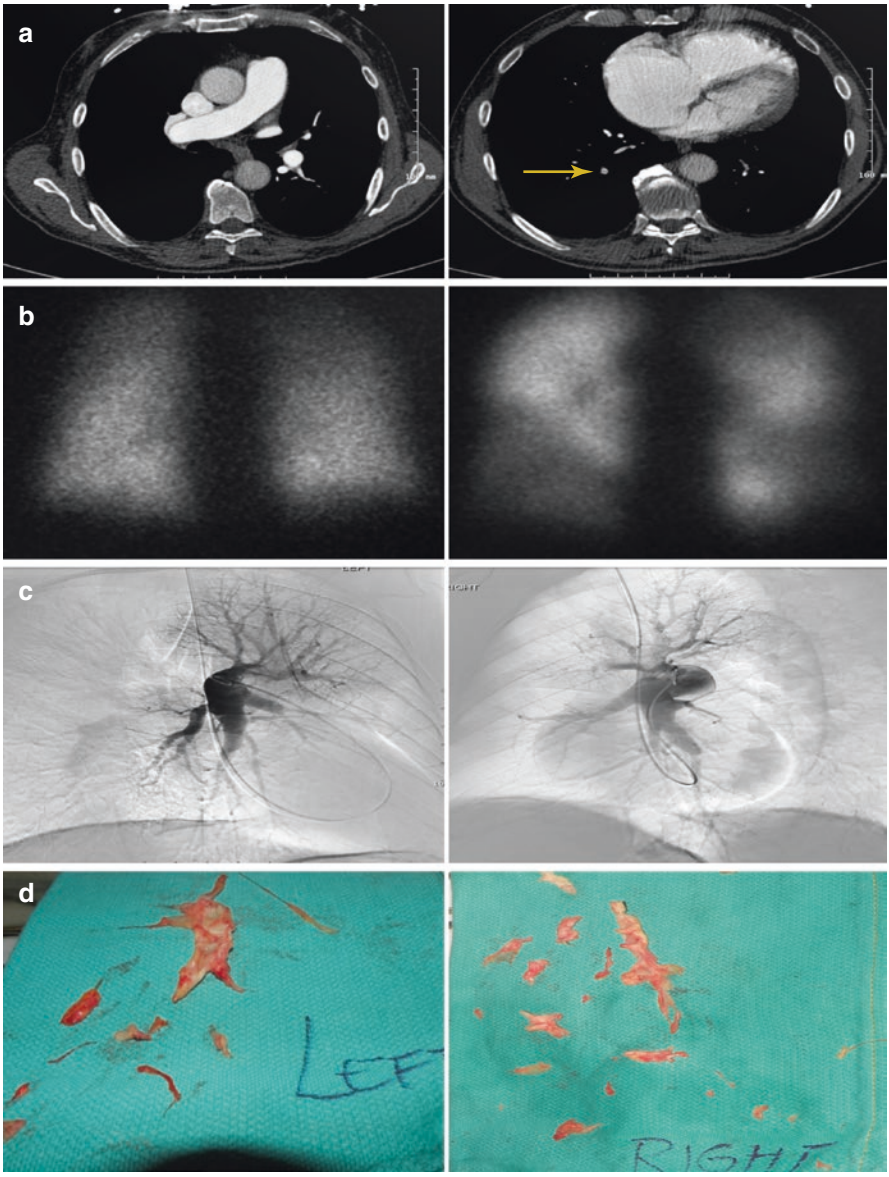

Fig. 4 A 64-year-old man without a history of previous PE presented with a 6-month history of progressive dyspnea on exertion and syncope. CT pulmonary angiography (**a**) was read as negative for PE, but upon closer inspection it showed distal segmental webbing in the right lower lobe (arrow). The VQ scan (**b**, posterior view; left ventilation; right perfusion), however, showed large mismatched perfusion defects that were easily recognized. Digital subtraction pulmonary angiography (**c**; left-right anterior oblique view; right-left anterior oblique view) clearly showed webbing and stenosis at the proximal segmental level in the lingula, left lower lobe, right middle, and right lower lobes. His mean pulmonary artery pressure (mPAP) was 59 mmHg, cardiac index 1.42 L/min/m^2, and pulmonary vascular resistance (PVR) 20 Wood units. The patient underwent pulmonary endarterectomy (specimens shown in panel **d**). Postoperatively, mPAP was 19 mmHg; CI, 2.9 L/min/m^2; and PVR, 3 Wood units

Digital Subtraction Angiography

Conventional invasive pulmonary angiography was instrumental in the understanding and treatment of CTEPH. Auger and colleagues published in 1992, a classic paper describing the angiographic findings suggestive of chronic thromboembolic disease included "pouching" defects, webs or bands, intimal irregularities, abrupt vascular narrowing, and complete vascular obstruction [59]. Figure 5 shows several examples of DSA in CTEPH. Advances in noninvasive imaging have allowed modalities such as CTPA to provide the same level of information with greater sensitivity and specificity for disease localized at the main, lobar, and proximal segmental level. However, for distal segmental and subsegmental disease, DSA can offer greater detail than CTPA (Table 2). In fact, in experienced CTEPH centers, if

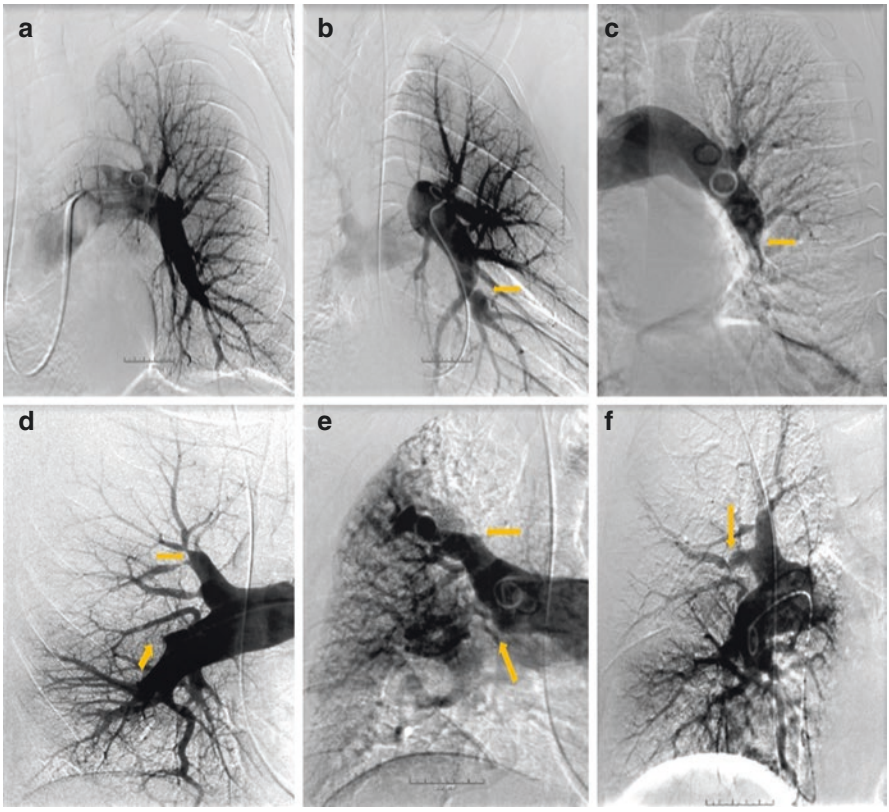

Fig. 5 CTEPH findings on digital subtraction angiography. Panels (**a**, **b**) show the importance of obtaining two views at 90 degrees of each other, in this case of the left lung (**a**, left anterior oblique; **b**, right anterior oblique). Only on right anterior oblique view, the stenosis with post-stenotic dilation in the left lower lobe becomes apparent. Pulmonary vascular abnormalities in CTEPH include narrowing (**c**), stenosis and abrupt cutoff (**d**), straight-edge stenosis and pouch-like defects (**e**), and band lesion (**f**)

the VQ scan shows large perfusion mismatched defects, but the CTPA is underwhelming, patients will be further evaluated with a DSA to ensure that the patient is not a surgical candidate (Fig. 5). Furthermore, with the advent of balloon pulmonary angioplasty, DSA has experienced a resurgence, particularly using supra-selective angiography to detect lesions that might be amenable to BPA In addition to this, advanced endovascular techniques such as cone-beam CT and optimal coherence tomography (OCT) can offer exquisite anatomic detail of CTEPH lesions that might clarify the diagnosis, but most importantly, may make BPA as a viable treatment option.

Magnetic Resonance Angiography (MRA)

Magnetic resonance imaging has undergone vast improvements over the last few years, particularly with regard to a shorter acquisition time and ability to perform high-resolution MR pulmonary angiography. As it is yet to find a clear foothold in the workup of CTEPH, its use is currently evolving. The sensitivity and specificity of magnetic resonance angiography (MRA) compared to CTPA and DSA can be seen in Table 2. MRI does not involve the use of ionizing radiation and also has the ability to perform a morphologic and functional assessment of the right ventricle [60]. The future role of MRA in the diagnosis and follow-up of CTEPH will be dependent on further studies. At this time, technical demands and suboptimal evaluation of lung parenchyma likely currently limit the use of MRI as the modality of choice. Because of its higher spatial resolution and faster imaging times (enabling better breath-holding), CT is also the preferred modality for segmental vasculature assessment compared to MRI.

Right Heart Catheterization

It is imperative to assess the presence of pulmonary hypertension and hemodynamics by virtue of a right heart catheterization. A mean pulmonary artery pressure (mPAP) of $\geq$20 mmHg denotes the presence of pulmonary hypertension and a PVR > =3 Wood units constitutes pre-capillary PH [2]. Careful assessment of the severity of elevation in PVR is critical, as treatment decisions are influenced by the severity of PH and whether or not it is concordant with the thrombotic burden observed on imaging. In CTED, resting hemodynamics are normal, but patients exhibit an abnormal pulmonary vascular hypertensive response to exertion, defined as a multipoint mPAP/CO slope > 3 mmHg/min/L during exercise or an mPAP > 30 mmHg plus total pulmonary resistance (TPR) > Wood units at maximal exercise [61, 62].

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) provides for a robust method to functionally assess patients who have a suspicion for CTEPH or CTED. It usually entails exercising on a treadmill or cycle ergometer while minute ventilation (VE) and expiratory gas concentrations are measured for oxygen uptake (VO2) and carbon dioxide output (VCO2) throughout the respiratory cycle. Ineffective gas exchange in CTEPH and CTED is reflected by hyperventilation. Specifically, the increased VE/VCO2 slope and dead space fraction (Vd/Vt) have been proven to be the best determinants for CTEPH [63]. In particular, CPET can have an important role in the workup of CTED by correlating the patient's dyspnea with ineffective gas exchange and increased dead space fraction while excluding other conditions such as ventilatory limitation and deconditioning.

Mimickers of CTEPH

Not all patients with an abnormal VQ scan will have CTEPH, as other conditions may be associated with a positive VQ scan. These conditions include in situ thrombosis, pulmonary artery sarcoma, fibrosing mediastinitis, pulmonary vasculitis, and sarcoidosis among others [64]. Although these conditions cannot always be distinguished from CTEPH using a VQ scan, as seen in Table 3, they have certain characteristic features on testing that can help differentiate them from CTEPH.

Table 3 Conditions that can mimic CTEPH

CTEPH mimicker	Findings on		
	echo	CTPA	VQ, PET, MRI
In situ thrombus	Can detect intra-cardiac shunts but may miss anomalous venous return, sinus venosus defects, or patent ductus arteriosus	Characteristic feature is neovascularization or the formation of small intrapulmonary vessels in the subpleural region near the centrilobular arterioles. Appears as a lining thrombus attached to the artery wall	Does not show perfusion defects on VQ
Pulmonary artery sarcoma	Pulmonary regurgitation secondary to involvement of the leaflets by the tumor, PAS can be seen moving with the cardiac cycle if it is attached to the wall at one place	Heterogeneously enhancing low-attenuation filling defect with frequently occupying the entire diameter of the pulmonary artery trunk or the main pulmonary arterial branches causing expansion of the involved arteries, contour, cauliflower-like polypoidal appearance, wall eclipse sign (arising from the wall of the artery eclipsing it at least on one side)	Demonstrate increased FDG uptake PET scans whereas CTEPH does not show PET avidity

Table 3 (continued)

CTEPH mimicker	Findings on		
	echo	CTPA	VQ, PET, MRI
Fibrosing mediastinitis	Elevated right ventricular systolic pressure	Diffuse infiltrative soft tissue process in the mediastinum that may also extend to the bilateral hila and the pulmonary parenchyma, extensive mediastinal calcification, compression of multiple structures in addition to the pulmonary arteries	On MRI, mass of heterogeneous signal intensity with decreased signal intensity on T2-weighted images is suggestive of fibrosis
Pulmonary vein stenosis	Not sensitive	Venous stenotic lesions	Multiple mismatched perfusion defects on VQ scan
Pulmonary venous occlusive disease	Right heart strain findings associated with PH	Smooth interlobular septal thickening, ground glass centrilobular opacities, and mediastinal adenopathy	VQ scan often normal
Sarcoidosis	Right heart strain findings associated with PH in patients with pulmonary sarcoid resulting in PH	Mediastinal lymphadenopathy and parenchymal involvement	Limited utility in differentiating from CTEPH

Abbreviations: *CTPA* computed tomography pulmonary angiography, *MRI* magnetic resonance imaging, *VQ* Ventilation/perfusion scintigraphy, *PET* Positron-emission tomography

Conclusions

CTEPH is a rare, yet under-recognized disease associated with considerable morbidity and mortality. Early and appropriate diagnosis is critical, as effective treatment options exist. One or more episodes of acute PE initiate the disease process, yet the exact incidence of CTEPH after acute PE is not known. Current sensible estimates suggest that within 2 years after acute PE, approximately 1–2% of patients could develop CTEPH. Importantly, at least a quarter of CTEPH patients do not have a history of PE, so a high index of suspicion is needed in patients with otherwise unexplained dyspnea or functional limitation. The diagnostic evaluation should include a VQ scan to look for mismatched perfusion defects and echocardiography to assess for PH. CTEPH is confirmed with pulmonary angiography, typically by CT and/or DSA, and with RHC. Advanced imaging modalities and exercise testing are occasionally needed to fine-tune the diagnosis and optimize treatment decisions. Considerable expertise and experience are necessary, and early referral to an expert CTEPH center is recommended.

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Medical, Endovascular, and Surgical Treatment of CTEPH

Kim M. Kerr and William R. Auger

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a result of unresolved pulmonary emboli that cause obstruction of the pulmonary vascular bed, elevated pulmonary vascular resistance, and right heart failure. CTEPH has long been recognized as predominantly a surgical disease and pulmonary thromboendarterectomy (PTE), also called pulmonary endarterectomy (PEA), cures 79% of patients [1], with perioperative mortality rates ranging from 2.2% to 5.2% at experienced centers [2, 3]. Guidelines from the 2015 European Society of Cardiology/European Respiratory Society [4] and the World Symposium on Pulmonary Hypertension 2018 [5] recommend that PTE be offered to all eligible CTEPH patients. Balloon pulmonary angioplasty (BPA) and/or pulmonary hypertension (PH)-targeted medical therapies are treatment options for patients with inoperable CTEPH or those with residual pulmonary hypertension following PTE surgery (Fig. 1).

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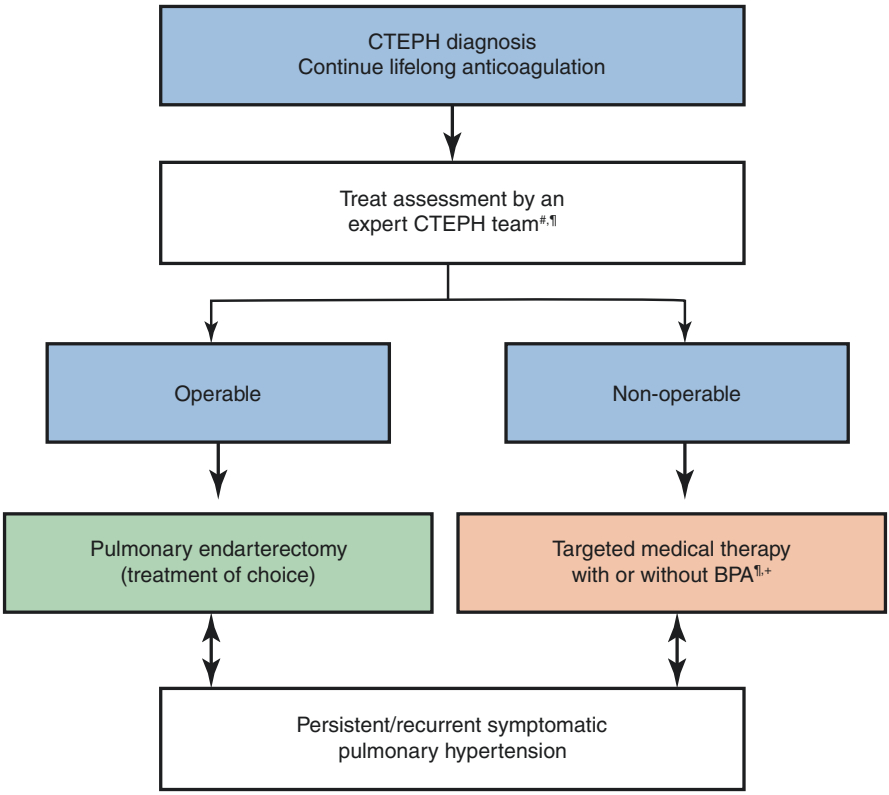

Fig. 1 Chronic thromboembolic pulmonary hypertension (CTEPH): revised treatment algorithm. BPA balloon pulmonary angioplasty. * multidisciplinary: pulmonary endarterectomy surgeon, PH expert, BPA interventionist and radiologist; ¶treatment assessment may differ depending upon the level of expertise; +BPA without medical therapy can be considered in selected cases

Surgical Treatment

Surgical treatment of CTEPH is very different from a surgical embolectomy that is performed for acute pulmonary embolism. Unlike an acute embolus, the organized fibrotic material of CTEPH is incorporated into the wall of the pulmonary artery. Consequently, a successful surgical resection requires a careful endarterectomy by an experienced surgeon of the clot that usually extends into the segmental and subsegmental arteries. Early reports of PTE surgery demonstrated this procedure to be an effective treatment for CTEPH, but it was associated with high mortality rates with significant postoperative morbidities. With greater diagnostic capabilities, the expansion of surgical experience, and refinements in the surgical technique over the years, both complication and mortality rates have steadily

declined. Short- and long-term studies have confirmed PTE to be an effective technique resulting in an improvement in cardiopulmonary hemodynamics, quality of life, and survival [6–9]. Because of the demonstrated long-term success of PTE, and as it is the only procedure that offers the potential for cure, multiple guidelines recommend that all patients with CTEPH be assessed for potential surgical treatment at an expert center [4, 5].

Establishing surgical candidacy is divided into two separate processes, the evaluation of technical operability and an assessment of perioperative risk against anticipated clinical benefit. Technical operability depends upon both the anatomic location of the chronic thromboembolic disease and the skill and experience of the surgeon, with the more central the clot the easier the procedure. If the clot burden originates at the segmental or subsegmental level, the more challenging is the endarterectomy.

Once it is determined that a patient has a technically operable disease, an assessment of whether surgery might result in symptomatic and/or pulmonary hemodynamic improvement is of paramount importance. This includes correlation between the amount of surgically accessible chronic thromboembolic material, severity of the pulmonary hypertension and right heart dysfunction, and the patient's symptoms. Historically, mean pulmonary artery pressure $\geq$ 25 mmHg and PVR > 300 dynes.sec.cm^{-5} in symptomatic patients were accepted indications for PTE surgery. However, there is increasing interest in a subgroup of patients with dyspnea and chronic thromboembolic disease but who do not have pulmonary hypertension at rest. Referred to as CTED, these patients may be symptomatic due to an elevation in dead space ventilation or an abnormal hemodynamic response to exercise. An inappropriate rise in mean pulmonary artery pressure, a decrease in pulmonary artery compliance, and a decreased O_2 pulse has been described in CTED patients when compared to controls. Evaluation of these patients with cardiopulmonary exercise testing and invasive exercise hemodynamics can assist in identifying those who may benefit from PTE surgery [10–12].

An estimate of perioperative risk is the next essential step in determining surgical candidacy. There are very few absolute contraindications to PTE surgery and these are confined to patients with a limited life expectancy from a comorbidity such as advanced malignancy and severe parenchymal lung disease in regions expected to be reperfused with surgery. Patients without a history of DVT or PE, are in right heart failure, are functional class IV, have a PVR > 1200 dyn.sec.cm^{-5}, inconsistency in imaging modalities, no appreciable lower lobe disease or significant concomitant lung or left heart disease are at an elevated risk with a less predictable long-term outcome, but these features are not contraindications to surgery [5]. The decision to proceed with surgery is relatively straightforward in otherwise healthy patients with mild to moderate symptoms and a central burden of chronic thromboembolic disease, but most patients are more complex and require the evaluation by an experienced, multidisciplinary team in determining surgical candidacy.

PTE surgery is performed via median sternotomy on cardiopulmonary bypass (CPBP) using profound hypothermic circulatory arrest. Despite diversion of blood away from the pulmonary arteries while on CPBP, circulatory arrest (pausing CPBP for up to 20 minutes) is required to prevent back-flow from systemic to pulmonary artery collateral vessels and obtain a bloodless surgical field during the endarterectomy. To prevent organ injury, the body is cooled to 20 °C and the head and heart are wrapped in a cooling jacket [7, 13].

Hemodynamic improvement is seen immediately after surgery and can be appreciated by echocardiography [14, 15] and hemodynamics obtained by a pulmonary artery catheter [2, 3]. Patients are typically extubated within 48 hours and discharged from the hospital within 14 days following surgery, in the absence of complications.

Postoperative complications unique to PTE surgery include residual pulmonary hypertension, airway hemorrhage, and hypoxemia due to either reperfusion edema or the V/Q mismatch that occurs following PTE surgery.

Airway hemorrhage may be due to surgical injury of the pulmonary artery or severe reperfusion edema. This complication is fortunately rare with a reported incidence of 2–6% [16, 17]. Most airway hemorrhage can be managed by reversing anticoagulation, but when more severe, placement of a bronchial blocker and/or extracorporeal life support (ECLS) may be required.

Hypoxemia is quite common following PTE surgery, not only due to the usual atelectasis seen following thoracic surgery, but also a redistribution of blood flow from previously well-perfused segments to newly perfused endarterectomized segments, referred to as pulmonary artery "steal." It is hypothesized that changes in regional pulmonary vascular resistance and loss of normal vasoregulatory mechanisms are responsible for the steal phenomenon that can be seen on postoperative nuclear perfusion scans [18–21]. A potentially life-threatening cause of postoperative hypoxemia is the development of reperfusion edema (RPE). This is a high-permeability edema that occurs in areas that have been reperfused as a result of PTE [22, 23]. The incidence ranges from 10% to 84% depending upon the definition used and the study cohort [3, 24, 25]. This complication typically occurs in the first 48 hours following surgery with more severe preoperative pulmonary hypertension and the presence of postoperative pulmonary hypertension identified as risk factors for the development of RPE. Treatment is primarily supportive and includes diuresis to reduce lung water, avoiding a high cardiac output, and a short course of corticosteroids based upon anecdotal experience and studies suggesting an inflammatory component to RPE [23, 26]. Severe cases may require ECLS for support [27–29]. RPE is typically self-limited, but it is a major cause of post-PTE mortality.

Persistent pulmonary hypertension (PH) following PTE surgery may be due to an inadequate endarterectomy, the small vessel arteriopathy that coexists with the large vessel obstructive component in CTEPH patients, or reversible factors such as hypercarbia, hypoxemia, and/or reperfusion edema. Postoperative residual PH is associated with increased perioperative mortality, although it can improve over time. A study from a single institution showed that patients with a residual pulmonary vascular resistance (PVR) of >500 dynes/sec/cm−5 experienced a mortality of 10.3% compared to a mortality of 0.9% in those with a postoperative PVR < 500 dynes/sec/cm−5 [2].

Treatment of persistent PH in the immediate perioperative period focuses on minimizing oxygen consumption, reversing hypoxemia and hypercarbia, optimizing right ventricular preload, and inotropic support. Systemic pulmonary artery vasodilators are typically avoided in the early postoperative period due to their potential to contribute to systemic hypotension and exacerbate ventilation-perfusion mismatching and hypoxemia. Reduction in PVR and/or improvement in oxygenation can be accomplished in some patients with inhaled nitric oxide or iloprost without an associated decrease in blood pressure [30–32]. Severe cases may require ECLS as a bridge to transplant or support during recovery [27–29].

Modest residual PH is not uncommon following PTE surgery, but the majority of these patients experience significant functional and symptomatic improvement with no apparent adverse effect on medium-term survival [1, 33]. A recent longer-term study of 880 subjects who underwent PTE in the United Kingdom was performed due to the observation that there is only a moderate correlation between the immediate postoperative hemodynamics and those obtained 3–6 months after surgery. They found that 51% of patients had an mPAP >25 mmHg on right heart catheterization at 3–6 months post-PTE, but the majority of patients maintained a good functional status in the long term. However, those with a mean PAP $\geq$ 30 mmHg were more likely to have PH therapy initiated, and a mean PAP $\geq$ 38 mmHg and PVR $\geq$ 425 dynes.sec.cm^{-5} at reassessment correlated with a worse long-term survival [34].

Based upon these data, it is appropriate in most postoperative PTE patients with residual PH to wait at least 3 months and reassess functional status and pulmonary hemodynamics with right heart catheterization before initiating treatment with PH-targeted therapy. However, those who clearly did not experience any significant hemodynamic improvement following surgery and those with ongoing right ventricular failure may benefit from earlier initiation of PH-targeted therapy.

Despite these complications, in-hospital mortality is quite low at experienced centers. The UC San Diego group has reported a 2.2% in-hospital mortality with long-term survival rates of 82% at 5 years and 75% at 10 years [2]. Long-term survival data from the international prospective registry showed that patients who underwent PTE surgery had an improved 3-year survival rate when compared to those who did not undergo surgery [9] and a recent study from a single study demonstrated 83% 5-year survival in patients who underwent surgery vs 55% in those offered surgery, but declined [35]. Limitations of both these studies are that they are observational and predate the availability of riociguat or BPA.

Balloon Pulmonary Angioplasty

Balloon pulmonary angioplasty (BPA), also referred to as percutaneous transluminal pulmonary angioplasty, was first described in CTEPH as a case report [36] followed by a small series of 18 patients in 2001 [37]. The modest pulmonary hemodynamic benefits attained, along with high complication rates, including one death, stifled an enthusiastic adoption of this treatment modality. However, a decade later, several case series published out of Japan demonstrating positive early

outcomes led to a renewed interest in the use of BPA for the treatment of CTEPH [38–40]. With evolving techniques and growing evidence for efficacy in selected CTEPH patients, the 2015 European Society of Cardiology/European Respiratory Society CTEPH treatment guidelines [4] as well as the treatment algorithm from the 2018 World Symposium on Pulmonary Hypertension [5] now recommend BPA as a therapeutic option for those patients who are not candidates for surgery or suffer from residual pulmonary hypertension after PTE surgery.

Unlike PTE surgery, where the chronic thromboembolic material is removed, BPA reduces vascular obstruction by forcing the material to the side of the wall, making the lumen larger. This can be associated with dissection of the tunica media and thinning of the vessel wall [41]. These thin-walled arteries expand over time due to exposure to the pulmonary artery pressure, leading to further increase in diameter of the vessel and preventing restenosis [42]. Hence, BPA is unlike coronary or peripheral artery angioplasty, where revascularization of a single vessel can result in immediate relief of symptoms but frequently requires stenting to prevent restenosis. With ongoing vessel expansion after BPA, pulmonary hypertension improves over weeks rather than immediately after a BPA session, but stenting is not required. BPA typically requires treatment of multiple segments and lobes over time to realize clinical improvement. Patients typically require four to six sessions, spaced apart over days to weeks. PH-targeted medical therapy is often combined, and frequently initiated, prior to BPA [43].

Data supporting the use of BPA in the treatment of CTEPH are limited to observational studies. BPA improves symptoms, exercise capacity, hemodynamics, and right ventricular function as reported in short- and medium-term follow-up studies. However, these studies consistently demonstrate improvement in 6 MWD and functional class in addition to pulmonary hemodynamics with significant reductions in mPAP, PVR, and BNP with improvement in cardiac index and right ventricular function after BPA [38, 39, 40, 44–48]. Improvement in oxygenation, in addition to hemodynamic improvement, has also been reported following BPA [49, 50].

Longer-term BPA data are starting to emerge. Results from a retrospective registry of seven institutions in Japan that included 1408 BPA procedures in 308 patients reported overall survival of 96.8% at 1 and 2 years and 94.5% at 3 years, after the initial BPA procedure. Follow-up right heart catheterization was performed on 196 patients at a mean of 426 ± 281 days after the final BPA procedure, revealing that the pulmonary hemodynamic improvements were maintained and the use of supplemental oxygen and PH medications was significantly reduced [50] (Table 1).

The major complications of BPA are related to reperfusion pulmonary edema (RPE) and vascular injuries arising from wire perforation or angioplasty and include dissection, hemorrhage, or perforation. RPE was reported to be as high as 53–60% in early studies [38, 41]. The complication rate reported in the Japanese multicenter registry is high, occurring in 36.3% of all procedures. Eight patients (3.9%) died within 30 days after BPA (three from sepsis, two from multiorgan failure, two from right heart failure, and one from an unknown cause). Severe complications requiring mechanical ventilation occurred in 5.5% and 2.9% required ECMO. Pulmonary artery perforation, dissection, or rupture was reported in 3.4%, hemoptysis was seen

Table 1 Japanese multicenter BPA registry results

	Baseline (n = 308)	After BPA (n = 249)	At follow-up (n = 196)	P value
WHO FC	3	2	2	<0.001
6MWD, m	318 ± 122	410 ± 105	430 ± 108	<0.001
mPAP, mmHg	43.2 ± 11.0	24.3 ± 6.4	22.4 ± 5.4	<0.001
Cardiac index	2.6 ± 0.8	2.9 ± 0.7	2.8 ± 0.6	<0.001
PVR, dyne.sec.cm−5	854 ± 451	360 ± 223	288 ± 194	<0.001
Patients on PH-targeted therapy	72%	58%	45%	<0.001

Ogawa et al. [50]

in 14%, and pulmonary injury (diagnosed by infiltrate on CXR or CT after BPA) seen in 17.8% [50]. Refinements in the technique to minimize the risk of reperfusion edema and vessel injury have resulted in a decrease in complication rates and improvement in outcomes at experienced centers. A recent meta-analysis of BPA studies published prior to February 2017 reported that early mortality of BPA ranged from 0% to 14.3% and lung injury occurred in 7.0–31.4% [51]. Risk factors identified for the development of RPE include first procedure, severity of pulmonary hypertension, and level of plasma B-type natriuretic peptide [52]. More recently, it is thought that many cases with pulmonary infiltrates or hemoptysis classified as having RPE may have actually suffered from vascular injury instead [41, 53]. As with PTE surgery, several studies have shown that the safety and efficacy of BPA improves over time with operator experience and innovation in lesion selection and procedure techniques [38, 45].

Medical Therapy

Lifelong anticoagulation is recommended for all CTEPH patients to prevent recurrent thrombosis and the greatest experience has been with vitamin K antagonists. Direct oral anticoagulants (DOACs) have proven to be effective in the treatment of acute venous thromboembolism, but a large prospective study has not yet been done to compare vitamin K antagonists to DOACs in the CTEPH population [54].

Drugs found to be effective in the treatment of pulmonary arterial hypertension (PAH) have been used off-label for many years to treat patients with CTEPH who are inoperable or suffer from residual or recurrent pulmonary hypertension following PTE surgery. Histologic changes in the distal vascular bed, similar to that seen in PAH patients, have been demonstrated in specimens from CTEPH patients [55–57]. CTEPH is not only a macroscopic disease of proximal obstructing chronic thrombi but is also associated with more distal small vessel remodeling, which explains residual pulmonary hypertension in patients who have otherwise undergone a complete endarterectomy. The presence of these small vessel changes provides the rationale for pulmonary hypertension (PH)-targeted therapy in patients with inoperable CTEPH and those with residual or recurrent pulmonary hypertension.

There have been several, randomized, double-blind, placebo-controlled trials of PH-targeted therapy in CTEPH that have demonstrated benefit in either pulmonary vascular resistance, 6 minute walk distance (6MWD), or functional class (FC), but at the time of this writing, only riociguat, a soluble guanylate cyclase stimulator, is FDA-approved for the treatment of inoperable CTEPH or residual/recurrent pulmonary hypertension following PTE surgery. The CHEST-1 study [58] demonstrated improvement in 6MWD, PVR, FC, and NT-proBNP in the treatment group compared to placebo in both the inoperable CTEPH and residual pulmonary hypertension groups and follow-up studies have shown this benefit to be sustained over time [59]. Other, prospective, randomized trials are listed in Table 2. A recent trial of the endothelin receptor antagonist macitentan (MERIT-1) in patients with inoperable CTEPH also demonstrated improvement in 6MWD and PVR at 16 weeks in the treatment group compared to the placebo group [60]. Unlike the CHEST study, patients who were Functional Class III or IV could also be on background therapy. Additional clinical benefits were seen with the addition of macitentan to the background therapy in this study, raising the possibility that combination therapy may be of benefit in CTEPH, as has been demonstrated in PAH. A more recent randomized trial of subcutaneous treprostinil in inoperable CTEPH patients also demonstrated an improvement in hemodynamics, 6MWD, functional class, and NT-pro BNP [61].

Table 2 Prospective randomized trials of PH-targeted therapy in CTEPH

	CHEST-1 [58]	MERIT-1 [60]	BENEFIT [63]	CTREPH [61]
Patients total Inoperable PH after PTE	261 189 (72.4%) 72 (27.6%)	80 80 (100%) 0 (0%)	157 96 (70.1%) 41 (29.9%)	105 Both groups enrolled, numbers not reported
Treatment	Riociguat	Macitentan	Bosentan	SQ treprostinil, target 30 ng/kg/min
Control	Placebo	Placebo	Placebo	SQ treprostinil, 3 ng/kg/min
Background PH-targeted therapy	No	Yes (61%)	No	Yes (30%)
Primary endpoint	Change 6MWD at 16 weeks	PVR at 16 weeks expressed as % baseline PVR	Change in PVR and 6MWD from baseline at 16 weeks	Change in 6MWD at 24 weeks
Results	Significant treatment effect on 6MWD (+ 46 m), PVR (−246 dynes.s. cm−5) as well functional class, NT-proBNP	Significant treatment effect on PVR (73% treatment vs 87.2% placebo) as well as 6MWD (+ 34 m)	Significant reduction in PVR (−24%), no significant improvement in 6MWD	Significant treatment effect on 6MWD (40.7 m)

Of note, none of these PH-targeted therapies have been studied in patients with operable CTEPH. Surprisingly, despite no evidence to tell us whether preoperative treatment of CTEPH with medical therapy improves or worsens surgical outcomes, a large number of patients are started on PH-targeted therapy prior to surgery. One observational study did demonstrate that medical treatment of operative CTEPH delayed referral for surgery but did not improve surgical outcomes [62]. Until we have definitive studies to guide their use, the practice of medical treatment of CTEPH prior to PTE surgery should be discouraged in most settings. Instead, early referral should be made to a surgical center for operability assessment.

Conclusion

Pulmonary thromboendarterectomy remains the standard of treatment for CTEPH, providing the best option for a cure of this form of pulmonary hypertension. Balloon pulmonary angioplasty and PH-targeted medical therapy are evolving treatment options for patients who are not surgical candidates or suffer from residual or recurrent pulmonary hypertension following PTE. Long-term multicenter data on the safety and efficacy of BPA and PH-targeted therapy are required to further guide the treatment of these patients.

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